Arabian Journal of Chemistry (2016) 9, 542–549

King Saud University

Arabian Journal of Chemistry

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Convenient synthesis of substituted pyrroles via a cerium (IV) ammonium nitrate (CAN)-catalyzed Paal–Knorr reaction

Ahmed Kamal [a,*], Shaikh Faazil [a], M. Shaheer Malik [a], Moku Balakrishna [a], Shaik Bajee [a], M. Rafique H. Siddiqui [b], Abdullah Alarifi [b]

[a] *Medicinal Chemistry and Pharmacology, CSIR-Indian Institute of Chemical Technology, Hyderabad 500 007, India*
[b] *Catalytic Chemistry Chair, Chemistry Department, College of Science, King Saud University, Riyadh 11451, Saudi Arabia*

Received 2 January 2013; accepted 4 April 2013
Available online 13 April 2013

KEYWORDS

Paal–Knorr reaction;
Cerium (IV) ammonium nitrate;
CAN;
Pyrrole;
γ-Diketone;
2,5-Dimethoxy-tetrahydrofuran

Abstract A screening of various cerium salts for promoting the Paal–Knorr pyrrole synthesis revealed the superiority of cerium (IV) ammonium nitrate (CAN) as a catalyst. Excellent yields of substituted pyrroles were obtained in CAN-catalyzed Paal–Knorr reactions of 1,4-diketones with various amines. The protocol is noteworthy for the mild reaction condition, short reaction times, scalability and easy isolation of products and high yields of the products.

1. Introduction

The pyrrole nucleus is, perhaps, the most important heterocycle abundantly found in bioactive natural molecules such as porphyrins and alkaloids (Katrizky, 2004; Sundberg, 1996). Pyrrole ring is also present in various drugs including many anti-inflammatants, immunosuppressants, COX-2 inhibitors, analgesic, antitubercular agents (Zhou and Giannakakou, 2005; Li et al., 1999; Doherty, 2004; Gribble, 1996; Biava et al., 2010) as well as the highly successful cholesterol-lowering drug atorvastatin (Lipitor, Fig 1), (Sawant and Maier, 2010). Additionally, pyrrole with 1,2,5-trisubstitution pattern exhibits remarkable biological properties as illustrated by the anti-inflammatory agents amtolmetin and tolmetin (Fig. 1), (Shue et al., 2004; Bertaccini and Coruzzi, 1998). As a result of their pharmaceutical significance, a number of methods have been developed for the preparation of substituted pyrroles. These include the Hantzsch reaction (Hantsch, 1890), conjugate addition reaction (Dieter and Yu, 2000), reductive coupling (Furstner et al., 1995), aza-Wittig reaction (Katrizky et al., 1994), and other multistep operations (Periasamy et al., 1999).

* Corresponding author at: Medicinal Chemistry and Pharmacology, CSIR-Indian Institute of Chemical Technology, Hyderabad 500 007, India. Tel.: +91 40 27193157; fax: +91 40 27193189.
E-mail addresses: ahmedkamal@iict.res.in (A. Kamal), faazilbagban@yahoo.co.in (S. Faazil), mdshaheermalik@gmail.com (M. Shaheer Malik), balakrishna.moku@yahoo.co.in (M. Balakrishna), bajee_shk@yahoo.co.in (S. Bajee), arifi@ksu.edu.sa (A. Alarifi).
Peer review under responsibility of King Saud University.

ELSEVIER Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.arabjc.2013.04.009
1878-5352

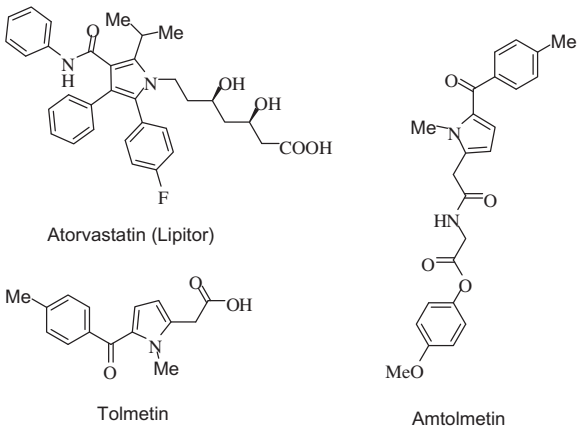


Figure 1 Some pyrrole-containing drugs.

However, the classical Paal–Knorr reaction, in which a 1,4 diketone is condensed with an amine, continues to be the most attractive method for the synthesis of pyrroles (Wang et al., 2004; Banik et al., 2005; Danks, 1999; Chen et al., 2006; Aghapoor et al., 2012). Despite its popularity, the Paal–Knorr reaction suffers from limitations such as drastic reaction conditions, high cost, poor yields, tedious workup and longer reaction time. Therefore, the development of milder and non-hazardous methods for pyrrole synthesis continues to be a very important area of investigation.

2. Results and discussion

In continuation of our ongoing investigations on the development of useful synthetic protocols suitable for applications in the field of combinatorial chemistry and chemistry-driven drug discovery (Kamal et al., 2007a,b, 2009, 2010) we undertook a study directed at developing cerium based catalysts for promoting the Paal–Knorr reaction under mild conditions. The results obtained in this study are presented in the following sections.

Cerium salts are inexpensive, soluble in many organic solvents, stable under aerobic condition and are less toxic. The most important cerium based reagent in organic synthesis is indubitably cerium (IV) ammonium nitrate (CAN), the usefulness of which was amply demonstrated by a wide array of synthetic transformations developed by Nair and Deepthi (2007).

The cerium salts selected for the study were cerium (III) chloride, cerium (IV) sulfate and CAN. They were screened as catalysts in the reaction between aniline **1** and hexane-2,5-dione **2** in methanol at room temperature and CAN emerged as a superior catalyst in terms of yields, catalyst loading and reaction time (Table 1).

In an attempt to find the optimum reaction conditions and to improve the overall efficiency of this CAN catalyzed Paal Knorr reaction, we examined the effect of the concentration of catalyst and the solvent used. It was observed that at a concentration of 5 mol percent, CAN provides the best results with 96% of pyrrole formation in 15 min. However, the decrease in concentration of CAN from 5% to 2.5% resulted in lower yields (Entry 7–8, Table 1). Additionally, the reaction was carried out in different organic solvents and a direct correlation between solubility of CAN (and polarity) and yield was observed (Toulene < CH_2Cl_2 < CH_3CN < EtOH < MeOH). The yields of product in different solvents are in a *fashion* as Toluene (yield: 35%) < CH_2Cl_2 (yield: 45%) < CH_3CN (yield: 75%) < EtOH (yield: 90%) < MeOH (yield: 96%)). Moreover, the reaction was also performed in the most polar solvent water, and the experimental yield after purification was 25%.

The optimized reaction conditions were then applied for the synthesis of a sortiment of 2,5-dimethyl pyrroles by the reaction of **2** with a series of aliphatic, heterocyclic and benzylic amines (Table 2). The addition of catalytic amount of CAN (5 mol%) typically resulted in the completion of the reaction within 10–20 min at ambient temperature. It is noteworthy that this protocol for the synthesis of pyrroles from polycyclic aromatic aniline (Table 2, Entry **g**) and heterocyclic amines (Table 2, Entry **j**, **l**, and **r**). Other notable pyrrole derivatives that were accessible by this method include N-phthalimido pyrrole **3i** and the bis-pyrrole **3k**. The use of nearly equimolar amounts of substrates in this protocol is advantageous when compared to the conventional methods that use excess of amine in order to promote the condensation (Curuni et al., 2003). Moreover, as no strong acid is used, the present method does not require neutralization after completion of the reaction. Finally, the method was scaled up to generate multigram quantities of pyrroles without any significant loss in yields.

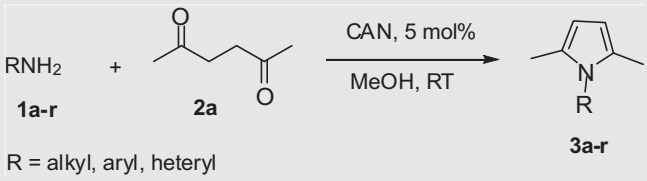
Diaryl pyrroles constitute an important and privileged structural motif in the context of medicinal chemistry applications (Biava et al., 2010). In order to access these valuable pyrrole derivatives, substituted aryl diketones were employed in the CAN-catalyzed condensations (Table 3). Pleasingly, the reactions afforded a number of diaryl pyrroles

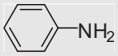
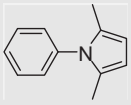
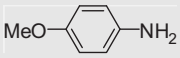
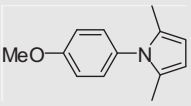
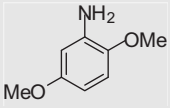
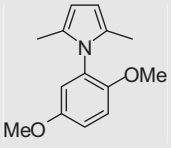
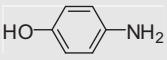
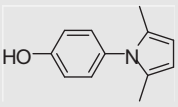
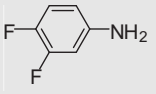
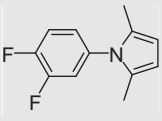
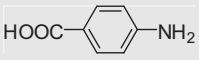
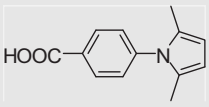
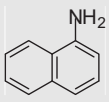
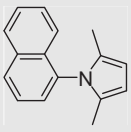
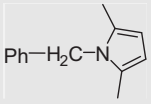
Table 1 Screening of the different cerium salts as catalysts for the reaction of aniline (**1**) with hexane-2-5-dione (**2**).

Entry	Catalyst (oxidation state)	Catalyst loading (mol%)	Time (h)	Yields (%)[a]
1	$CeCl_3$ (III)	20	24	45
2	$CeCl_3$ (III)	10	24	20
3	$Ce(SO_4)_2$ (IV)	20	3	35
4	$Ce(SO_4)_2$ (IV)	10	4	45
5	CAN (IV)	20	0.75	65
6	CAN (IV)	10	0.25	90
7	CAN (IV)	5	0.25	96
8	CAN (IV)	2.5	1	85
9	None	–	24	–

[a] Isolated yields after chromatography.

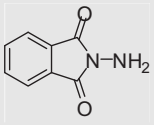
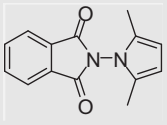
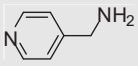
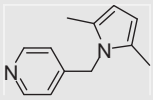
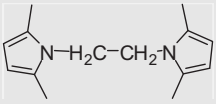
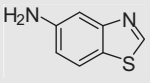
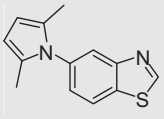
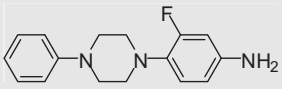
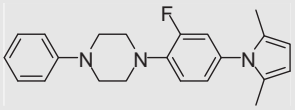
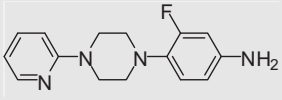
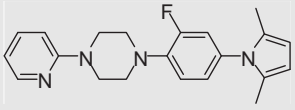
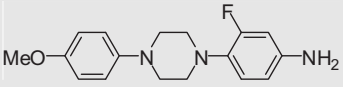
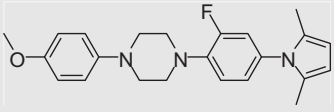
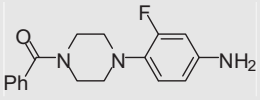
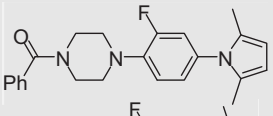
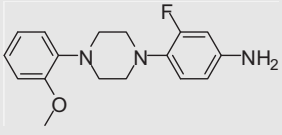
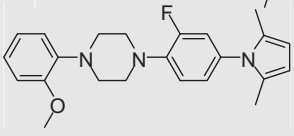
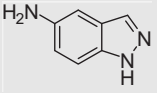
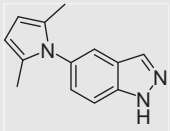
Table 2 Synthesis of 1,3,5-substituted pyrroles from primary amines (**1a–r**) and diketone **2a** using catalytic amount of CAN.



Entry	Substrate (1a-r)	Product (3a-r)	Time (min)	Yield (%)[a]
a			15	95
b			15	88
c			15	84
d			15	93
e			16	92
f			17	75
g			16	94
h	Ph–H_2C–NH_2		15	92

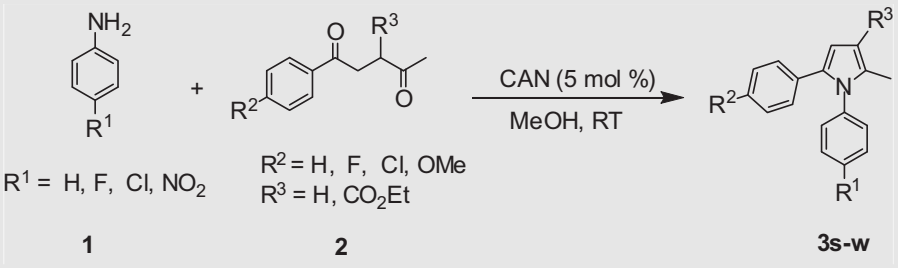
(*continued on next page*)

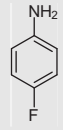
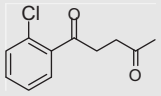
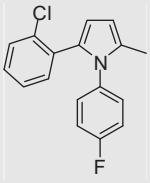
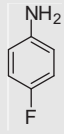
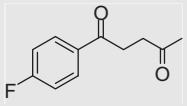
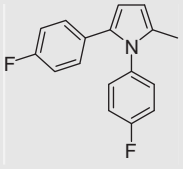
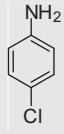
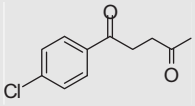
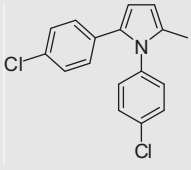
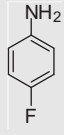
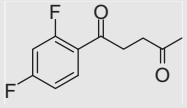
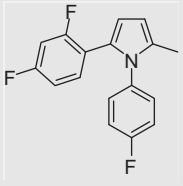
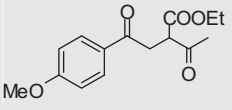
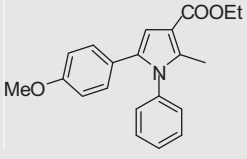
Table 2 (*continued*)

i			15	93
j			18	75
k[b]	$NH_2(CH_2)NH_2$		18	88
l			17	85
m			15	88
n			16	89
o			15	88
p			18	84
q			15	85
r			18	83

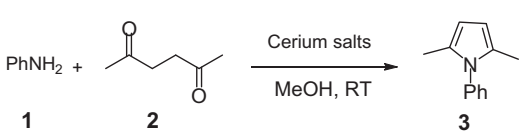
[a] Isolated yield after column chromatography.
[b] Two equivalents of diketone **2a** used.

Table 3 CAN-catalyzed synthesis of diaryl pyrrole from anilines and aryl diketones.

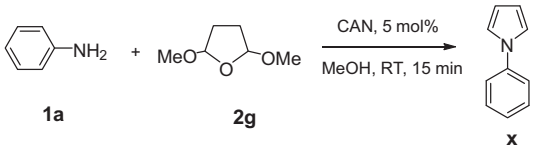


Entry	Amine	Diketone	Product	Time (min)	Yield (%)[a]
s				15	92
t				15	93
u				16	95
v				18	90
w				15	88

[a] Isolated yield after column chromatography.



Scheme 1 A.



Scheme 2 B.

in excellent yields under the optimal reaction conditions (Table 3).

Nair has reported that CAN effectively catalyzes the hydrolysis of acetals[21] and this property was exploited in a one-pot synthesis of N-substituted pyrrole (**1a**) from 2,5-dimethoxytetrahydrofuran (**2g**) and primary amines. It is presumable that CAN initially deprotects the acetal functionality and subsequently promotes the Paal–Knorr reaction (Scheme 2). (See Scheme 1).

3. Conclusion

In summary, the present CAN-catalyzed protocol provides a mild, efficient and practical variant of the Paal–Knorr pyrrole synthesis. Excellent yields of variously substituted pyrroles are obtained under ambient reaction conditions. Continued investigations to generate libraries of substituted pyrrole derivatives for applications in the field of chemistry-driven drug discovery are currently underway and the results will be reported in due course.

4. Experimental

4.1. General remarks

Melting points were determined with an electrothermal melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin–Elmer model 683 or 1310 spectrometers with sodium chloride optics. ^{1}H NMR spectra were recorded on an Avance 300 MHz spectrometer (Bruker, Fallanden, Switzerland) and ^{13}C NMR spectra were recorded on a UNITY 400 MHz (Varian, Switzerland). Chemical shifts (δ) are reported in ppm, downfield from internal TMS standard. Mass spectra were recorded using a quadruple ion trap mass spectrometer (Thermo Finnign, San Jose, CA, USA) equipped with an electro spray source.

4.2. A representative experimental procedure for pyrrole synthesis

To a solution of aniline (10 mmol) and hexane-2, 5-dione (10 mmol) in methanol (5 mL) at room temperature, cerium ammonium nitrate (0.5 mmol) was added. The mixture was allowed to stir at room temperature for 15 min and after the completion of reaction as indicated by TLC; the solvent was evaporated under reduced pressure. The residue was redissolved in ethyl acetate (30 mL) and washed with water (15 mL). The organic layer was dried using brine and traces of water were removed using anhydrous sodium sulfate and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography using EtOAc: petroleum ether (1:10) to afford the pure product.

4.2.1. 2,5-Dimethyl-1-phenyl-1H-pyrrole ***3a***

Solid, mp. 45–48 °C. IR (KBr): (υmax): 3098, 3054, 2972, 2922, 2738, 1960, 1596, 1495 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.03 (s, 6H), 5.9 (s, 2H), 7.21 (m, 2H), 7.36–7.43 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 12.85, 106.33, 127.81, 128.41, 128.84, 128.23, 139.18; LC–MS: m/z: 194 $(M + Na)^+$.

4.2.2. 1-(4-Methoxyphenyl)-2,5-dimethyl-1H-pyrrole ***3b***

Solid, mp. 55–57 °C. ^{1}H NMR (($CDCl_3$, 300 MHz): δ 2.0 (s, 6H), 3.72(s, 3H), 7.65 (d, J = 7.2 Hz, 2H), 7.87 (d, J = 7.2 Hz, 2H) ^{13}C NMR (100 MHz, $CDCl_3$): 12.5, 55.3, 105.4, 126.1, 127.7, 130.2, 156.9; LC–MS: m/z: 201 $(M + 1)^+$.

4.2.3. 1-(2,4-Dimethoxyphenyl)-2,5-dimethyl-1H-pyrrole ***3c***

Solid, mp. 50–52 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.97(s, 6H), 3.75(s, 3H), 3.87 (s, 3H), 5.89 (s, 2H), 6.55 (d, 1H, J = 8.90 Hz), 6.95 (s, 1H), 7.08 (d, 1H, J = 8.90 Hz); LC–MS: m/z: 232 $(M + 1)^+$.

4.2.4. 4-(2,5-Dimethyl-1H-pyrrol-1-yl)phenol ***3d***

Solid, mp. 39–42 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.01 (s, 6H), 5.87 (s, 2H), 6.88 (d, 2H, J = 6.14 Hz), 7.05 (d, 2H, J = 6.14 Hz); LC–MS: m/z: 188 $(M + 1)^+$.

4.2.5. 1-(3,4-Difluorophenyl)-2,5-dimethyl-1H-pyrrole ***3e***

Solid, mp. 55–57 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.01 (s, 6H), 5.82 (s, 2H), 7.2–7.3 (m, 3H). ^{13}C NMR (300 MHz) 12.5, 106, 108.2, 117.3(d), 125.8, 138.7, 146, 145.6; LC–MS: m/z: 208 $(M + 1)^+$.

4.2.6. 4-(2,5-Dimethyl-1H-pyrrol-1-yl)benzoic acid ***3f***

Solid, mp. 63–65 °C. IR (KBr): (υmax): 3439, 3058, 3054, 2921, 2855, 1960, 1650, 1516, 1442, 1263 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.05 (s, 6H), 5.84 (s, 2H), 7.31 (d, J = 8.309 Hz, 2H), 8.24 (d, J = 8.309 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): 13.03, 106.24, 127.77, 127.88, 128.15, 130.71, 143.51, 171.11; LC–MS: m/z: 216 $(M + 1)^+$.

4.2.7. 2,5-Dimethyl-1-(naphthalen-1-yl)-1H-pyrrole ***3g***

Solid, mp. 60–62 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.08(s, 6H), 5.91(s, 2H), 7.06(t, 1H, J = 7.93 Hz), 7.77 (t, 1H, J = 7.93 Hz), 7.82 (d, 1H, J = 8.12 Hz), 8.01 (d, 1H), 8.19, (d, 1H), 8.78 (d, 1H); LC–MS: m/z: 222 $(M + 1)^+$.

4.2.8. 1-Benzyl-2, 5-dimethyl-1H-pyrrole ***3h***

Solid, mp. 55–57 °C, ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.16(s, 6H), 5.02 (s, 2H), 5.80(s, 2H), 6.88 (d, 2H, J = 6.7 Hz), 7.27–7.32 (m, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): 11.64, 46.25, 105.36, 125.17, 126. 52, 127.56, 128.24, 138.07; LC–MS: m/z: 186 $(M + 1)^+$.

4.2.9. 2-(2,5-Dimethyl-1H-pyrrol-1-yl)isoindoline-1,3-dione ***3i***

Solid, mp. 103–105 °C. IR (KBr): (υmax): 3438, 3057, 2923, 1790, 1745, 1533, 1452, 1354, 1258, 1110 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.03 (s, 6H), 5.86 (s, 2H), 7.85–7.86 (d, J = 3.2 Hz, 2H), 7.97 (d, J = 3.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): d 10.49, 104.96, 123.84, 127.57, 129.10, 134.62, 164.24; LC–MS: m/z: 241 $(M + Na)^+$.

4.2.10. 4-((2, 5-Dimethyl-1H-pyrrol-1-yl)methyl)pyridine ***3j***

Solid, mp. 98–100 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.11 (s, 6H), 4.99(s, 2H), 5.87 (s, 2H), 6.78 (d, 2H, J = 5.21 Hz), 8.51 (d, 2H, J = 5.21 Hz). ^{13}C NMR 13.15, 46.16, 107.13, 121.14, 128.12, 148.59, 150.50; LC–MS: m/z: 187 $(M + 1)^+$.

4.2.11. 1,2-Bis (2,5-dimethyl-1H-pyrrol-1-yl)ethane ***3k***

Solid, mp. 60–62 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.96 (s, 12H), 3.9 (s, 4H), 5.65 (s, 4H). ^{13}C NMR: 12, 4, 43.60, 106, 129; LC–MS: m/z: 217 $(M + 1)^+$.

4.2.12. 5-(2,5-Dimethyl-1H-pyrrol-1-yl)benzo[d]thiazole ***3l***

Solid, mp. 100–102 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 205 (s, 6H), 5.94 (s, 2H), 7.36 (d, 1H, J = 8.30 Hz), 7.81 (d, 1H, J = 1.51 Hz), 8.19 (d, 1H, J = 8.30 Hz), 9.07 (s, 1H); LC–MS: m/z: 229 $(M + 1)^+$.

4.2.13. 1-(4-(2,5-Dimethyl-1H-pyrrol-1-yl)-2-fluorophenyl)-4-phenylpiperazine ***3m***

Solid, mp. 98–100 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.035 (s, 6H), 3.32 (t, 4H), 3.38 (t, 4H), 5.87 (s, 2H), 6.89–7.04 (m, 5H), 7.25 (s, 1H), 7.30 (2H); LC–MS: m/z: 351 $(M + 1)^+$.

4.2.14. 1-(4-(2,5-Dimethyl-1H-pyrrol-1-yl)-2-fluorophenyl)-4-(pyridin-2-yl)piperazine ***3n***

Solid, mp. 111–113 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2,03 (s, 6H), 3.27(t, 4H, J = 5.28, 4.53 Hz), 3.74 (t, 4H, J = 5.28, 3.74), 5.88(s, 2H), 6.74–6.65 (m, 2H), 6.9–7.05 (m, 3H), 7.52 (dt, 1H), 8.24 (dd, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 12.91, 44.40, 50.53, 105.60, 107.20, 113.69, 116.12, 116.48, 118.16, 118.72, 124.28, 124.32, 128.90,132.26, 137.38,145.98, 147.43; LC–MS: m/z: 351 $(M + 1)^+$.

4.2.15. 1-(4-(2,5-Dimethyl-1H-pyrrol-1-yl)-2-fluorophenyl)-4-(4-methoxyphenyl)piperazine ***3o***

Solid, mp. 114-116 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.05 (s, 6H), 3.28 (t, 4H, J = 5.52 Hz), 3.32 (t, 4H), 3.89 (s, 3H), 5.88 (s, 2H), 6.8 (d, 2H, J = 8.3 Hz), 6.90–7.06 (m, 5H); LC–MS: m/z: 380 $(M + 1)^+$.

4.2.16. (4-(4-(2,5-Dimethyl-1H-pyrrol-1-yl)-2-fluorophenyl)piperazin-1-yl)(phenyl) methanone ***3p***

Solid, mp. 107–109 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.02 (s, 6H), 5.87(s, 2H), 6.91–7.01 (m, 3H), 7.4 (m, 5H); LC–MS: m/z: 377 $(M + 1)^+$.

4.2.17. 1-(4-(2,5-Dimethyl-1H-pyrrol-1-yl)-2-fluorophenyl)-4-(2-methoxyphenyl)piperazine ***3q***

Solid, mp. 115–117 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.04 (s, 6H), 3.29 (t, 4H, J = 5.24 Hz), 3.35 (t, 4H, J = 4.198), 3.91 (s, 3H), 5.88 (s, 2H), 6.90 (d, 1H, J = 8.35 Hz), 6.95 (d, 1H, J = 8.35 Hz), 6.98 (s, 1H), 7.02 (dd, 1H, J = 6.29 Hz), 7.04, (dd, 1H, J = 8.35 Hz), 7.07 (d, 1H, J = 3.14 Hz); LC–MS: m/z: 380 $(M + 1)^+$.

4.2.18. 5-(2,5-Dimethyl-1H-pyrrol-1-yl)-1H-indazole ***3r***

Solid, mp. 120–122 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.02, (s, 6H), 5.97(s, 2H), 7.21 (d, 1H, J = 1.51 Hz), 7.24(s, 1H), 7.55(s, 1H), 7.58(s, 1H), 7.61(d, 1H, J = 1.51 Hz), 8.13(s, 1H); LC–MS: m/z: 212 $(M + 1)^+$.

4.2.19. 1-(4-Fluorophenyl)-2-methyl-5-(2-chlorophenyl)1H-pyrrole ***3s***

Solid, mp. 125–127 °C (yield 60%); ^{1}H NMR ($CDCl_3$, 300 MHz) 2.09 (s, 3H), 6.10–6.11(m, 1H), 6.28 (m, 1H), 6.96(2H, m), 7.03–7.10 (m, 4H), 7.25(m, 2H); LC–MS: m/z: 286 $(M + 1)^+$.

4.2.20. 1,2-Bis(4-Fluorophenyl)-5-methyl-1H-pyrrole ***3t***

Solid, mp. 113–116 °C. IR (KBr): (υmax): 3070, 2960, 2928, 2837, 2737, 2055, 1866, 1744, 1614, 1589, 1511, 1227 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.10 (s, 3H), 5.98 (d, J = 3.39 Hz, 1H), 6.19 (d, J = 3.39 Hz, 1H), 6.81 (t, 2H), 6.97–6.72 (m, 2H), 7.12 (m, 4H); ^{13}C NMR (100 MHz, CDCl3): 12.69, 76.13, 76.56, 76.99, 107.10, 108.12, 114.33, 114.62, 115.33, 115.63, d 128.99, d 129.56, 131.08, 132.78, d 134.72, 159.10, d 159.49, d 162.58; LC–MS: m/z: 270 $(M + 1)^+$.

4.2.21. 1,2-Bis(4-chlorophenyl)-5-methyl-1H-pyrrole ***3u***

Solid, mp. 115–117 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.10 (s, 3H), 6.29 (d, 1H, J = 2.32 Hz), 6.34 (d, 1H, J = 2.32 Hz), 6.94 (m, 2H), 6.97 (m, 2H), 7.03 (m, 2H), δ 7.10 (m, 2H); LC–MS: m/z: 303 $(M + 1)^+$.

4.2.22. 2-(2,4-Difluorophenyl)1-(4-fluorophenyl)-5-methylpyrrole ***3v***

Solid, mp. 119–121 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.15 (s, 3H), 6.11 (d, 1H, J = 3.7 Hz), 6.30 (dd, 1H, J = 3.7 Hz), 6.65–6.76 (m, 2H, J = 9.0 Hz), 7.04–7.00 (m, 2H), 7.12–7.05 (m, 3H, J = 5.2 Hz); LC–MS: m/z: 288 $(M + 1)^+$.

4.2.23. Ethyl 5-(4-Methoxyphenyl)-2-methyl-1-phenyl-1H-pyrrole-3-carboxylate ***3w***

Solid, mp. 111–115 °C C. IR (KBr): (υmax): 3438, 3057, 2923, 1790, 1745, 1533, 1452, 1354, 1258, 1110 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.15 (t, J = 6.81 Hz, 3H), 2.42 (s, 3H), 3.77 (s, 3H), 4.14 (q, J = 6.81 Hz, 2H), 6.60 (s, 1H) 6.81 (d, J = 8.51 Hz, 2H) 7.24–7.29 (m, 5H) 7.41 (d, J = 8.51 Hz, 2H) ^{13}C NMR (100 MHz, $CDCl_3$): d 10.49, 104.96, 123.84, 127.57, 129.10, 134.62, 164.24; LC–MS: m/z: 336 $(M + 1)^+$.

4.2.24. 1-Phenyl-1H-pyrrole ***3x***

Solid, mp. 40–43 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.26 (s, 2H), 7.00 (s, 2H), 7.17–7.32 (m, 5H); LC–MS: m/z: 144 $(M + 1)^+$.

Acknowledgments

The authors (SF, MB and SB) are thankful to Council of Scientific and Industrial Research (CSIR) for financial support under the XIIth Five Year plan project "Affordable Cancer Therapeutics" and for the award of fellowship to one of the authors (SB) and University Grant Commission (UGC) for the authors (SF and MB).

References

Aghapoor, Kioumars, Ebadi-Nia, Leila, Mohsenzadeh, Farshid, Morad, Mina Mohebi, Balavar, Yadollah, Darabi, Hossein Reza, 2012. J. Organomet. Chem., 708.

Banik, B.K., Banik, I., Renteriaa, M., Dasgupta, S.K., 2005. Tetrahedron Lett. 46, 2643.

Bertaccini, G., Coruzzi, G., 1998. Gastroenterology 114, 72.

Biava, M., Porretta, G.C., Poce, G., Battilocchio, C., Manetti, F., Botta, M., Forli, S., Sautebin, O. L., Rossi, A., Pergola, C., Ghelardini, C., Galeotti, N., Makovec, F., Giordani, A., Anzellotti, P., Patrignani, P., Anzini, M., 2010. J. Med. Chem. 53, 723 and references cited therein.

Chen, J., Wu, H., Zheng, Z., Jin, C., Zhang, X., Su, W., 2006. Tetrahedron Lett. 47, 5383.

Curuni, M., Montanari, F., Rosati, O., Lioy, E., Margarita, R., 2003. Tetrahedron Lett. 44, 3923.

Danks, T.N., 1999. Tetrahedron Lett. 40, 3957.

Dieter, R.K., Yu, H., 2000. Org. lett. 2, 283.

Doherty, A.M., 2004. Annual Reports in Medicinal Chemistry. Elsevier, Amstrdam, vol. 39.

Furstner, A., Weintritt, H., Hupperts, A., 1995. J. Org. Chem. 60, 6637.

Gribble, G.W., 1996. Comprehensive Heterocyclic Chemistry II. In: Katritzky, A.R., Rees, C.W., Scriven, E.F.V. (Eds.), Pergamon Press, Oxford, vol. 2, p. 207.

Hantsch, A., 1890. Ber. Dtsch. Chem. Ges. 23, 1474.

Kamal, A., Devaiah, V., Reddy, K.L., Rajendar, Shetti, R.V.C.R.N.C., Shankaraiah, N., 2007a. J. Comb. Chem, 267.

Kamal, A., Reddy, K.L., Devaiah, V., Shankaraiah, N., Reddy, G.S.K., Raghavan, S., 2007b. J. Comb. Chem. 9, 29.

Kamal, A., Nagula, M., Nagula, S.C., Reddy, R., Prabhakar, S., Reddy, C.S., Marcos, E.N., Leonardo, S.S., 2009. Chemistry (Weinheim an der Bergstrasse, Germany) 15, 7215.

Kamal, A., Ashwini, B.K., Suresh, P., Shankaraiah, N., Shiva Kumar, M., 2010. Bioorg. Med. Chem. Lett. 21, 350.

Katrizky, A.R., 2004. Chem. Rev. 125, 1042.

Katrizky, A., Jiang, J., Steel, P.J., 1994. J. Org. Chem. 59, 4551.

Li, Q., Sham, H.L., Rosenberg, S.H., 1999. Ann. Rep. Med. Chem. 34, 139.

Nair, V., Deepthi, A., 2007. Chem. Rev. 107, 1862, and references therein.

Periasamy, M., Srinivas, G., Bharati, P., 1999. J. Org. Chem. 64, 4204.

Sawant, P., Maier, Martin E., 2010. Tetrahedron 66, 9738.

Sheu, Ming-Thau, Wu, Jender, Chen, Chih-Jui, Chao, Su-Hui, Wua, An-Bang, 2004. Tetrahedron Lett. 45, 8107.

Sundberg, R.J., 1996. In Comprehensive Heterocyclic Chemistry. In: Katritzky, A.R., Rees, C.W., Scriven, E.F.V. (Eds.). Pergamon, Oxford, vol. 2, p. 119.

Wang, B., Gu, Y., Luo, C., Yang, T., Yang, L., Suo, J., 2004. Tetrahedron Lett. 45, 3417.

Zhou, J., Giannakakou, P., 2005. Curr. Med. Chem. Anticancer Agents 5, 65.