Organic Preparations and Procedures International
The New Journal for Organic Synthesis

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/uopp20

# Facile New Alternative Method for the Synthesis of 1-(3-Methyl-1-phenyl-1H-pyrazole-5-yl)piperazine from 1-Methylpiperazine and 1-Benzylpiperazine

Dnyanadeo J. Kesarkar, Bharat B. Kashid & Sunil S. Sukthankar

**To cite this article:** Dnyanadeo J. Kesarkar, Bharat B. Kashid & Sunil S. Sukthankar (2021) Facile New Alternative Method for the Synthesis of 1-(3-Methyl-1-phenyl-1H-pyrazole-5-yl)piperazine from 1-Methylpiperazine and 1-Benzylpiperazine, Organic Preparations and Procedures International, 53:2, 105-111, DOI: 10.1080/00304948.2020.1858688

**To link to this article:** https://doi.org/10.1080/00304948.2020.1858688

ORGANIC PREPARATIONS AND PROCEDURES INTERNATIONAL
2021, VOL. 53, NO. 2, 105–111
https://doi.org/10.1080/00304948.2020.1858688

Taylor & Francis
Taylor & Francis Group

EXPERIMENTAL PAPER



# Facile New Alternative Method for the Synthesis of 1-(3-Methyl-1-phenyl-1H-pyrazole-5-yl)piperazine from 1-Methylpiperazine and 1-Benzylpiperazine

Dnyanadeo J. Kesarkar[a], Bharat B. Kashid[b], and Sunil S. Sukthankar[a]

[a]Precise Chemipharma Pvt. Ltd., C-384, T.T.C, Indira Nagar, MIDC Industrial Area, Turbhe, Navi Mumbai, Maharashtra, India; [b]Chemistry Research Laboratory, School of Chemical Sciences, Solapur University, Solapur, India

**ARTICLE HISTORY** Received 18 March 2020; Accepted 2 August 2020

Pyrazole and its derivatives continue to be subjects of considerable importance due to their wide spectrum of biological applications.[1–7] For example, the Type 2 Diabetes (T2D) drug Teneligliptin hydrobromide incorporates a 1,3,5-substituted pyrazole moiety. Teneligliptin (**I**, Figure 1) was marketed under the trade name of Tenelia and approved in Japan in 2012 for treatment of T2D.[8–11] Teneligliptin has been well-received in the market, so synthetic chemists have focused considerable attention on the designing of new economical routes to produce this drug at scale while still meeting stringent quality requirements. The original synthetic route is certainly suitable for the production of gram quantities of the desired drug with the required quality; however, the need for timely and economical manufacture of this active pharmaceutical ingredient on multi-kilogram scale in the appropriate purity[12–15] motivated us towards the development of a new route. Crucial to this is the preparation of 5-piperazine pyrazole derivative (**6**, Scheme 1), an improved method for which is the subject of this report.

An examination of the available literature shows that prior preparations of **6** have had such drawbacks as the instability of starting materials,[16] use of expensive catalysts,[17] or the commercial unavailability of reactants.[18,19] In particular, the use of alkoxycarbonyl protecting groups leads to formation of impurities and decreased yield. In the same vein, there are also serious safety considerations, particularly with scale-up in mind.[20–23]

In our view, an important consideration for the preparation of **6** is the protection of the piperazine moiety with a methyl or benzyl group (Scheme 1). Our synthesis of **6** begins with commercially available 1-methyl- or 1-benzylpiperazine, **1** or **1'**, respectively. In the first stage, a solution of *t*-butyl acetoacetate in refluxing toluene is prepared. Using a Dean-Stark apparatus for the removal of generated *t*-butanol, slow addition of N-methylpiperazine produces ketoamide **2** (95%) (or **2'** for the benzylic case). The ketoamide is then treated with phenylhydrazine hydrochloride to obtain compound **3** (or **3'**) as its hydrochloride salt. Compound **3** is then cyclized with $POCl_3$ to obtain the protected pyrazole **4** (or **4'**). The protected pyrazole is treated with ethyl

**CONTACT** Dnyanadeo J. Kesarkar dnyaneshwar_kesarkar@rediffmail.com Precise Chemipharma Pvt. Ltd., C-384, T.T.C, Indira Nagar, MIDC Industrial Area, Turbhe, Navi Mumbai, Maharashtra 400703, India

Supplemental data for this article can be accessed here.

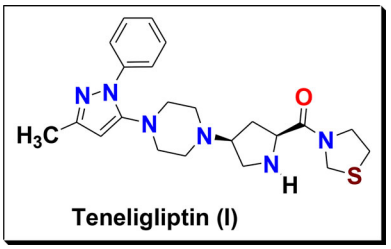
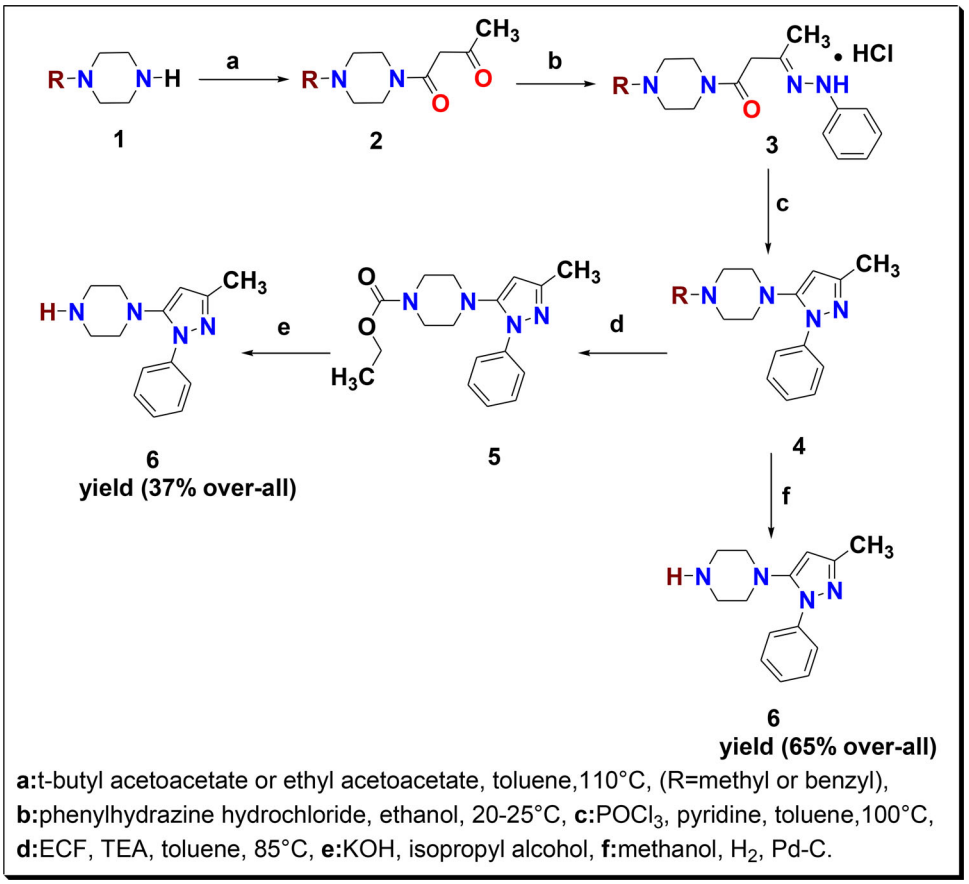



**Figure 1.** The T2D drug Teneligliptin.




**Scheme 1.** Synthesis of key intermediate **6**.

chloroformate in the presence of triethylamine to obtain carbamate **5**. Compound **5** is subsequently hydrolyzed in ethanolic KOH to produce the crucial intermediate **6**. Alternatively, if R is a benzyl group, compound **6** is obtained by debenzylation of the related benzylic congener **4'** in the presence of $H_2$/Pd-C, and the hydrogenation catalyst

**Table 1.** Screening of reagents for the conversion of **3** into **4**.

| Entry | Reagents | Reaction in hours | Safety, workup, and remarks | % yields |
|---|---|---|---|---|
| 1. | Lawesson's Reagent | 8 | Toxic, degradation of product during reaction, tedious workup, expensive reagent and THF solvent for reaction. | 40 |
| 2. | $P_4S_2$ | 10 | Toxic, tedious workup, more time, less conversion, | 50 |
| 3. | $P_2S_5$ | 5 hr | Toxic, less time, good conversion, expensive reagent and THF as solvent. | 80 |
| 4. | $POCl_3$ | 4 | Industrially feasible, less time, very good conversion, affordable reagent, recoverable and reusable toluene as solvent. | 88 |

may be recovered and re-cycled. All of the novel compounds in this method were fully characterized (see Experimental section).

As part of our work, we screened different cyclization reagents for the conversion of **3** into **4**, and the results are reported in Table 1.

Our new preparation avoids the use of labile protecting groups and thus has the potential to improve the impurity profile of the key intermediate **6**. The method uses commercially available reactants and does not require the use of highly unstable, expensive or hazardous reagents. It is our hope that these preparative advances will facilitate the upgraded production of the important active pharmaceutical ingredient, Teneligliptin.

## Experimental section

All of the raw materials used were procured from commercial manufacturing sources. Reagent grade materials were purchased from Sigma Aldrich. Solvents were purchased from Merck and SD Fine Chemicals. We used palladium on carbon (10%) from Hindustan Platinum Pvt. Ltd. The FT-IR spectra were determined on a Perkin Elmer Spectrum 100 instrument using the KBr pellet technique. $^1$H NMR spectra were obtained at 500 MHz, on a Bruker Avance instrument. Chemical shifts ($\delta$) were determined using TMS as the internal standard. HPLC-Mass analyses were performed on a Shimadzu 2020 apparatus. Thin-layer chromatography (TLC) was done with Merck TLC Silica Gel 60 F254 (0.25 mm) plates visualized by UV light at 254 nm and iodine vapor. Elemental analyses were obtained using a Perkin Elmer 2400 CHNS/O Series II System (100V) elemental analyzer. Melting points were determined on a Mettler Toledo apparatus and are uncorrected.

### *1-(4-Methylpiperazine-1-yl)butane-1,3-dione (2)*

*t*-Butyl acetoacetate (20.00 kg, 126.43 mol) and toluene (92.0 L) were heated up to 110 °C. We then added 1-methylpiperazine (**1**, 11.5 kg, 114.81 mol), and the reaction mixture was stirred at the same temperature for 5.5 hours. Completion of reaction was confirmed by TLC ($CHCl_3$:$CH_3OH$ 90:10). The reaction mass was cooled to 60 °C and distilled under reduced pressure (700 mm Hg) at 60-65 °C to obtain **2**, 20.12 kg, 95%,

brown viscous oil, TLC Rf 0.50 ($CHCl_3$:$CH_3OH$ 90:10). IR ($cm^{-1}$): 2940, 2799, 1722, 1635, 1448, 1295, 1143. $^1$H-NMR (DMSO-d6): $\delta$ 2.17-2.14 (s, 3H, $COCH_3$), 2.24-2.22 (s, 2H), 2.27-2.25 (t, 4H), 3.32-3.29 (t, 2H), 3.45-3.42 (s, 2H, CO-$CH_2$-CO), 3.62 (s, 3H, N-$CH_3$); $(M+H)^+$: m/z = 184.9.

*Anal.* Calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.21. Found: C, 58.61; H, 8.72; N, 15.26.

### 1-(4-Methylpiperazine-1-yl)-3-(2-phenylhydrazilidine)butane-2-one hydrochloride (3)

1-(4-Methylpiperazine-1-yl)butane-1,3-dione (**2**, 20.00 kg, 108.55 mol) was dissolved in 200 L ethanol and the reaction mixture cooled at 20-25 °C; phenylhydrazine hydrochloride (16.34 kg, 151.1 mol) was added slowly such that the temperature did not exceed 25 °C. After the addition, the reaction mixture was kept at 25-30 °C for 12 hours. Completion of reaction was confirmed by TLC ($CHCl_3$:$CH_3OH$ 90:10). The solid was filtered off and washed with ethanol to obtain **3**, as its hydrochloride salt, 29.15 kg, 86%, cream colored solid, mp 159 °C, TLC Rf 0.19 ($CHCl_3$:$CH_3OH$ 90:10). IR ($cm^{-1}$): 3433, 2996, 2927, 2434, 1661, 1596, 1515, 1488, 1452, 974, 759. $^1$H-NMR (DMSO-d6): $\delta$ 1.89 (s, 3H), 2.69 (s, 3H), 3.40-3.14 (t, 4H), 3.73-3.58 (t, 4H), 3.89 (s, 2H, -CO-$CH_2$-C = N); 7.17-6.67 (m, 5H), 8.86 (C = N-NH-Ar), 11.33 (s, 1H, -N-NH·HCl); $(M+H)^+$: m/z = 274.9.

*Anal.* Calcd for $C_{15}H_{22}N_4O$: C, 65.67; H, 8.08; N, 20.42. Found: C, 65.74; H, 8.06; N, 20.39.

### 1-Methyl-4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazine (4)

1-(4-Methylpiperazine-1-yl)-3-(2-phenylhydrazylidine)butane-2-one hydrochloride (**3**, 29.00 kg, 93.3 mol) was suspended in 58.0 L toluene. Then 29.0 L of pyridine was added. The mixture was heated to 100 °C, $POCl_3$ (30.44 kg, 198.5 mol) was added and the reaction mass heated for 4 hours at 100 °C. Completion of reaction was confirmed by TLC ($CHCl_3$:$CH_3OH$ 90:10). The reaction mass was cooled to 30 °C and 10% NaOH solution was added to pH 12. The product was extracted into ethyl acetate and washed with brine. Evaporation gave **4**, 21.01 kg, 88%, off white solid, 89 °C, TLC Rf 0.62 ($CHCl_3$:$CH_3OH$ 90:10). IR ($cm^{-1}$): 3062, 2959, 2927, 1594, 1559, 1502, 1448, 905, 770. $^1$H-NMR (DMSO-d6): $\delta$ 2.14 (s, 3H), 2.17 (s, 3H), 2.75-2.35 (t, 4H), 2.78-2.77 (t, 4H), 5.78 (s, 1H), 7.74-7.24 (m, 5H); $^{13}$C NMR (DMSO-d6): $\delta$ 152.10, 148.79, 140.21, 128.78, 126.11, 122.51, 94.00, 54.56, 50.86, 46.02, 14.05; $(M+H)^+$: m/z = 257.1.

*Anal.* Calcd for $C_{15}H_{20}N_4$: C, 70.28; H, 7.86; N, 21.86. Found: C, 70.20; H, 7.90; N, 21.90.

### 1-(3-Methyl-1-phenyl-1H-pyrazol-5-yl)piperazine (6)

1-Methyl-4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazine (**4**, 18.00 kg, 70.21 mol), triethylamine (4.25 kg, 42.0 mol) and 72.0 L toluene was heated at 80 °C. Then ethyl chloroformate (7.92 kg, 72.98 mol) was slowly added to the reaction mixture. The reaction mixture was refluxed for 2 hours. Completion of reaction was confirmed by TLC. Then 180.00 L of

water was added slowly at 30-35 °C. The organic layer was separated and the aqueous layer was washed with 90.00 L of toluene. The combined organic layers were washed with 90.00 L water. The organic layer was dried over anhydrous sodium sulfate. After filtration, the solvent was distilled out under reduced pressure (700 mm Hg) to obtain ethyl 4-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazine-1-carboxylate **5**, 21.0 kg, 95%, TLC Rf 0.66 ($CHCl_3$:$CH_3OH$ 95:5). The mass was dissolved in 90.00 L isopropyl alcohol. To this was added potassium hydroxide (29.81 kg, 53.23 mol). The reaction mixture was refluxed for 4 hours. The solvent was distilled out under reduced pressure (700 mm Hg). To the mass thus obtained was added 180.00 L of water at 30-35 °C. The reaction mixture was stirred for 2.5 hours at 15-20 °C. The crystallized product was filtered off and washed with 36.00 L water. The wet solid was dried under vacuum at 50-55 °C for 5.5 hours to obtain **6**, 14.97 kg, 88%, off-white solid, mp 107 °C, TLC Rf 0.20 ($CHCl_3$:$CH_3OH$ 90:10), HPLC purity 99.5%. IR ($cm^{-1}$): 3398, 2834, 2822, 1596, 1559, 1503, 1457, 915, 774.3. $^1$H-NMR (DMSO-d6): $\delta$ 2.14 (s, 3H), 2.69 (t, 4H), 2.70 (t, 4H), 3.40 (s, 1H), 5.76 (s, 1H); 7.76-7.24 (m, 5H). $(M + H)^+$: m/z = 242.9.

*Anal.* Calcd for $C_{14}H_{18}N_4$: C, 69.39; H, 7.49; N, 23.12. Found: C, 69.46; H, 7.45; N, 23.09.

### *1-(4-Benzylpiperazin-1-yl)butane-1,3-dione (2')*

Using N-benzylpiperazine (1.744 kg, 4.5 mol) and t-butylacetoaceate (1.721 kg, 10.88 mol) in the same manner as described above for **2**, we obtained **2'**, 2.45 kg, 95%, brown viscous oil, TLC Rf 0.52 ($CHCl_3$:$CH_3OH$ 90:10). $^1$H-NMR (DMSO-d6): $\delta$ 1.69 (s, 2H), 2.14 (s, 3H), 2.74-2.69 (t, 8H), 4.55 (s, 2H, N-$CH_2$-Ar), 7.28-7.24 (t, 1H), 7.46-7.42 (m, 2H), 7.76-7.74 (m, 2H).

*Anal.* Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.27; H, 7.70; N, 10.80.

### *3-(2-Phenylhydrazono)-1-(4-benzylpiperazin-1-yl)butan-1-one hydrochloride (3')*

Using compound **2'** (2.45 kg, 9.41 mol) and phenylhydrazine hydrochloride (1.90 kg, 13.1 mole) in the same manner as described for **3** above, we obtained **3'**, as its hydrochloride salt, 3.24 kg, 89%, as a pale yellow solid, mp 210 °C, TLC Rf 0.22 ($CHCl_3$:$CH_3OH$ 90:10).

*Anal.* Calcd for $C_{21}H_{26}N_4O$: C, 71.97; H, 7.48; N, 15.99. Found: C, 71.93; H, 7.55; N, 16.02.

### *1-Benzyl-4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazine (4')*

Using compound **3'** (2.0 kg, 5.17 mol) and $POCl_3$ (2.65 kg, 17.28 mol) we prepared 1-benzyl-4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazine **4'**, 1.45 kg, 84%, brown viscous oil, TLC Rf 0.58 ($CHCl_3$:$CH_3OH$ 90:10). $^1$H-NMR(DMSO-d6): $\delta$ 1.86 (s, 3H), 2.35-2.30 (s, 4H), 3.30 (s, 2H, N-$CH_2$-Ar), 3.45 (t, 4H), 6.68-6.66 (s, 1H), 7.04-7.02 (m, 2H), 7.16-7.12 (t, 2H), 7.26-7.22 (m, 2H), 7.33-7.28 (m, 4H).

*Anal.* Calcd for $C_{21}H_{24}N_4$: C, 75.87; H, 7.28; N, 16.85. Found: C, 75.80; H, 7.30; N, 16.90.

### *1-(3-Methyl-1-phenyl-1H-pyrazol-5-yl)piperazine (6) from Compound 4' via Hydrogenolysis*

1-Benzyl-4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazine (**4'**, 1.0 kg, 3.0 mol) was dissolved in 10.0 L methanol at 30 °C in an autoclave. The apparatus was flooded with nitrogen and 100 g of Pd-C was added to the reaction mixture. A pressure of hydrogen (4 kg/cm$^2$) was applied at 45-50 °C for 8 hours. Completion of reaction was confirmed by TLC, and the reaction mass was cooled to 30 °C. The autoclave was flooded with nitrogen and the catalyst was filtered off. The filtrate was concentrated under vacuum (700 mm Hg) to obtain1-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazine **6**, 0.67 kg, 92%, as an off white solid, mp 107 °C, TLC Rf 0.20 ($CHCl_3$:$CH_3OH$ 90:10), HPLC purity 99.2%. $^1$H-NMR (DMSO-d6): $\delta$2.14 (s, 3H), 2.74-2.69 (t, 8H), 4.55 (s, 1H), 5.77 (s, 1H), 7.28-7.24 (t, 1H), 7.46-7.42 (t, 2H), 7.76-7.74 (d, 2H). $(M+H)^+$: m/z = 242.9.

*Anal.* Calcd for $C_{14}H_{18}N_4$: C, 69.39; H, 7.49; N, 23.12. Found: C, 69.35; H, 7.55; N, 23.10.

## Acknowledgments

The authors are thankful to the management of Precise Chemipharma Pvt. Ltd., for providing the opportunity to explore this research work and the Analytical Development Laboratory for continuous analysis support.

## References

1. S. P. Singh, Om Prakash and R. K. Vaid, *Indian J. Chem.*, **23B**, 191 (1998).
2. V. K. Ahluwalia, V. K. Garag and A. Gupta, *Indian J. Chem.*, **33B**, 761 (1964).
3. K. A. Rao, J. N. Gadreand and S. Pednekar, *Indian J. Chem.*, **36B**, 410 (1997).
4. D. Bhaskar Reddy, N. Subbha Reddy and T. Balaji, *Indian J. Chem.*, **23B**, 983 (1984).
5. V. J. Ram and M. Nath, *Indian J. Chem.*, **33**, 1048 (1994).
6. H. M. Virupakshaiah, M. B. Talawar, U. V. Laddi, Y. S. Somannavar, V. V. Badiger and S. C. Bennur, *Ind. J. Het. Chem.*, **6**, 63 (1996).
7. X. Zhang, J. Kang, P. Niu, J. Wu, W. Yu and J. Chang, *J. Org. Chem.,* **79**, 10170 (1997). doi: 10.1021/jo501844x
8. N. Kumar, S. R. Devineni, K. Aggile, P. R. Gajjala, P. Kumar and S. K. Dubey, *Res. Chem.,* **44**, 567 (2018). doi:10.1007/s11164-017-3120-3
9. J. Bronson, A. Black, T. G. Murali Dhar, B. A. Ellsworth and J. A. Merritt, *Ann. Rep. Med. Chem.*, **48**, 471 (2013).
10. M. Goda and T. Kadowaki, *Drugs Today (Barc)*, **49**, 615 (2013). doi:10.1358/dot.2013.49.10.2035882
11. T. Yoshida, F. Akahoshi, H. Sakashita, M. Nakamura, S. Sonda, M. Takeuchi, Y. Tanaka, S. Sekiguchi, T. Ishige, K. Shima, M. Nabeno, Y. Abe, J. Anabuki, A. Soejima, Y. Takashina and Y. Hayashi, *Bioorg. Med. Chem.,* **20**, 5705 (2012). doi:10.1016/j.bmc.2012.08.012
12. T. Yoshida, H. Sakashita, N. Ueda, S. Kirihara, S. Uemori, R. Tsutsumiuchi and F. Akahoshi, US2011/0282058 A1 (2011).
13. F. Akahoshi and K. Shinji, WO2012/165547 A1 (2012).

14. M. K. Suresh, P. K. Bipin, V. K. Ramachandran, P. P. Jayant, Y. Venkataramana Reddy, N. B. Shailendra, P. C. Uddhav, D. P. Ulhas and B. B. Shekhar, WO2014/041560 A2 (2014)
15. T. Wang, J. F. Kadow, Z. Zhang, Z. Yin, N. A. Meanwell, A. Regueiro-Ren, J. Swidorski, Y. Han, D. J. Carini and L. G. Hamann, US2008/0139572 A1 (2008).
16. H. Kitajima, H. Sakashita, F. Akahoshi and Y. Hayashi, US Patent 7, 074, 794, (2006).
17. Z. Hongwen and Z. Qiang, WO2012/099915 (2012).
18. A. K. Kapoor, D. C. Barman, A. Nath and Mohan Prasad, WO/2015/063709A1 (2015).
19. S. Zhichun, H. Dandan, J. Yuwei and Z. Xiaoqing, CN104177295A (2014).
20. P. Giri, A. Tendolkar, A. K. Kapoor, D. C. Barman, A. Nath and M. Prasad, WO/2015/019239 (2015).
21. K. Hiroshi, S. Hiroshi, A. Fumihiko and H. Yoshiharu, WO/2002/014271 (2002).
22. Z. Baofu, X. Jijun, G. Qiang, Z. Xianshu, L. Shufang and L. Haiwang, CN102675321A (2012).
23. S. S. Sukthankar and D. J. Kesarkar, Indian Patent 2016/21027674 A (2016).