Journal of the Serbian Chemical Society

JSCS-info@shd.org.rs • www.shd.org.rs/JSCS

J. Serb. Chem. Soc. *84* (3) 237–244 (2019)
JSCS–5179

UDC 547.772.2+537.5–962:615.28
Original scientific paper

Microwave-assisted synthesis and antimicrobial evaluation of 6-[3-aryl-1-phenyl-4′,5′-dihydro[4,5′-bi-1*H*-pyrazol]-3′-yl]-2*H*-chromen-5-ols

DONGAMANTI ASHOK[1]*, RANGU KAVITHA[1], SRINIVAS GUNDU[1] and MADDERLA SARASIJA[2]

[1]*Green and Medicinal Chemistry Laboratory, Department of Chemistry, Osmania University, Hyderabad- 500 007, India and* [2]*Department of Chemistry, Satavahana University, Karimnagar- 505001, India*

(Received 6 December 2017, revised 7 December, accepted 21 December 2018)

Abstract: A new series of 6-[3-aryl-1-phenyl-4′,5′-dihydro[4,5′-bi-1*H*-pyrazol]-3′-yl]-2*H*-chromen-5-ol derivatives was synthesized by Michael addition of chalcones **5a**–**j** with hydrazine hydrate in presence of sodium acetate under conventional heating and microwave irradiation. Structural assignment of the products was confirmed based on IR, ^{1}H-NMR, ^{13}C-NMR, MS and analytical data. All the synthesized compounds **6a**–**j** were screened for their antimicrobial activity against various bacterial and fungal strains. Most of the compounds exhibited variable range of antimicrobial activity and compounds **6c**–**f** and **6i** showed promising antimicrobial potency.

Keywords: pyrazole; pyrazoline; microwave irradiation; antimicrobial activity.

INTRODUCTION

Heterocyclic compounds containing nitrogen and oxygen play important roles in agrochemical and pharmaceuticals. Heterocyclic compounds have great applicability in pharmaceutics because they have specific chemical reactivity and provide false synthons in biosynthetic processes or block the normal functioning of biological receptors. The interesting biological activities of heterocycles have stimulated considerable research work in recent years, including the synthetic utility. Pyrazoles, an important member of heterocyclic compounds, are widely found as the core structure in a large variety of compounds that possess important agrochemical and pharmaceutical activities. Many pyrazole derivatives are reported to have a broad spectrum of biological activities, such as anti-inflammatory,[1,2] antifungal,[3] herbicidal,[4] insecticidal,[5] anti-HIV,[6] antiviral,[7] anticonvulsant[8] and anticancer[9] activities. Some of the drugs possessing a pyrazole scaf-

*Corresponding author E-mail: ashokdou@gmail.com
https://doi.org/10.2298/JSC171206113A

fold, such as celecoxib,[10] rimonabant,[11] deracoxib,[12] and phenylbutazone, exhibiting anti-inflammatory, analgesic and antipyretic activities, are already on the market (Fig. 1).

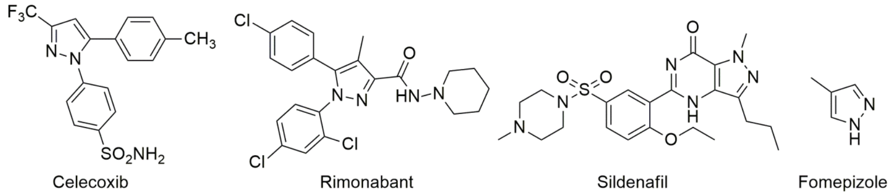


Fig. 1. Commercially available pyrazole and pyrazoline drugs.

Pyrazolines are partially reduced form of pyrazoles that contain five-membered ring system with two adjacent nitrogens. Pyrazolines are one of the emerging classes of compounds associated with a broad spectrum of biological activities. Many compounds bearing pyrazoles and their reduced forms pyrazolines constitute an interesting class of heterocycles due to their synthetic versatility and effective biological activities, such as antiviral,[13] anti-inflammatory,[14,15] antitubercular,[16] anti-amoebic,[17] analgesic,[18] antibacterial,[19] analgesic,[20] antifungal,[21] anti-arthritic,[22] cerebroprotective[23] and antidepressant[24] activities. They are also useful as biodegradable agrochemicals.[25]

A literature survey revealed several synthetic protocols for the synthesis of these compounds and the presence of this core in any molecule plays a key role in enhancing activity. Prompted by the above-mentioned biological properties of pyrazole and pyrazoline incorporated heterocycles, it was contemplated to synthesize a novel series of pyrazole–chromene containing pyrazolines. In continuation to ongoing research, herein, the synthesis of 6-[3-aryl-1-phenyl-4′,5′-dihydro[4,5′-bi-1*H*-pyrazol]-3′-yl]-2*H*-chromen-5-ol derivatives in excellent yields is reported.

EXPERIMENTAL

Materials

All used materials were obtained commercially, mostly from Sigma–Aldrich, and were used without further purification.

Equipment

All the microwave irradiation experiments were performed in a CEM Discover microwave system equipped with an IR sensor, with which the reaction temperatures were monitored. All the reactions were monitored on silica gel percolated TLC plates, 60 F254 from Merck and the spots were visualized with UV light. Melting points were determined by the open capillary method and are uncorrected. The ^{1}H-NMR and ^{13}C-NMR spectra were run on a Bruker Avance-400 spectrometer at 400 and 100 MHz, respectively, using tetramethylsilane (TMS) as an internal reference. Mass spectra were recorded on a Shimadzu LCMS 2020 mass spectrometer. Elemental microanalysis was performed on a Perkin Elmer CHN-2400 analyzer.

Spectral and analytical data of the synthesized compounds are given in Supplementary material to this paper.

*General procedure for the synthesis of 6-[3-aryl-1-phenyl-4',5'-dihydro[4,5'-bi-1*H*-pyrazol]-3'-yl]-2*H*-chromen-5-ol derivatives (**6a**–**j**)*

Conventional heating method. To a solution of 3-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)-1-(5-hydroxy-2*H*-chromen-6-yl)prop-2-en-1-ones **5a**–**j** (0.23 mmol) in DMF (5 mL) containing sodium acetate (0.23 mmol) and hydrazine hydrate (0.23 mmol), few drops of acetic acid was added and the reaction mixture heated at 80–90 °C for 1–3 h. The progress of the reaction was monitored by TLC. After completion of the reaction, ice-cold water was added. The solid product that separated was filtered, washed with water and dried. Recrystallisation from MeOH:$CHCl_3$ (1:1) afforded 6-[3-aryl-1-phenyl-4′,5′-dihydro[4,5′-bi-1*H*-pyrazol]-3′-yl]-2*H*-chromen-5-ols **6a**–**j**. Yield: 57–62 %.

Microwave irradiation method. A mixture of 3-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)-1-(5-hydroxy-2*H*-chromen-6-yl)prop-2-en-1-ones **5a**–**j** (0.23 mmol), hydrazine hydrate (0.23 mmol), sodium acetate (0.23 mmol) and few drops of acetic acid in DMF (2 mL) was taken in a glass vessel and then placed into a teflon vial with screw cap and the mixture was subjected to microwave irradiation at 100 W for 1–3 min. After completion of the reaction, indicated by TLC, the vial was cooled and the reaction mixture was poured into ice cold water. The solid product that separated was filtered, washed with water and dried. Recrystallisation from MeOH:$CHCl_3$ (1:1) furnished 6-[3-aryl-1-phenyl-4′,5′-dihydro[4,5′-bi-1*H*-pyrazol]-3′-yl]-2*H*-chromen-5-ol derivatives **6a**–**j**. Yield: 86–96 %.

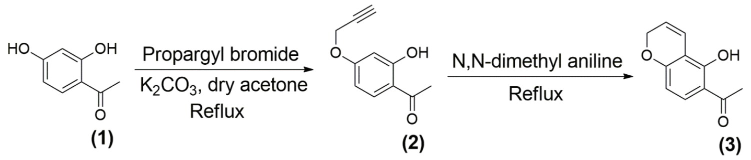
Biological assays

Antibacterial activity. The synthesized novel compounds **6a**–**j** were screened for their antibacterial activity against different types of bacterial strains, *viz*. Gram-positive bacterial strains *Staphylococcus aureus* and *Bacillus subtilis*, and Gram-negative bacterial strains *Escherichia coli* and *Proteus vulgaris* at concentrations of 10 and 20 μg mL^{-1}. The cultures were diluted with 5 % saline, autoclaved, and the final volume was made with a concentration approximately 10^5–10^6 CFU mL^{-1}. The synthesized compounds were diluted in acetone for the antibacterial biological assays. For agar disk diffusion method,[26] the solution form of a test compound was allowed to air-dry, such that the disk became completely saturated with the test compound. The saturated chemical disks were introduced onto the upper layer of the medium evenly floated with the bacteria. The disks were dipped in different chemical samples and placed over the evenly spread bacterial nutrient media and incubated at 37 °C for 24–48 h for better inhibition of the bacteria. The zones of inhibition were measured after 24–48 h. All the experiments were performed in triplicate, and the results are expressed as zone of inhibition in mm. The zones of inhibition of synthesized compounds were compared with the zone of inhibition of the standard antibiotic gatifloxacin at concentrations of 10 and 20 μg mL^{-1}.

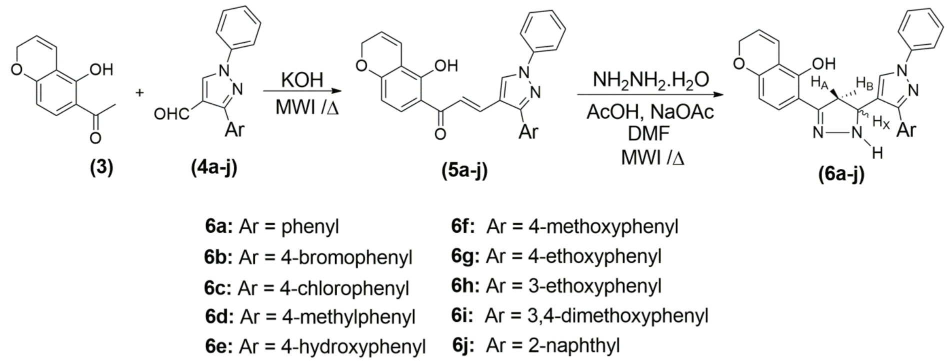
Antifungal activity. The antifungal activities of the synthesized compounds **6a**–**j** were tested against three pathogenic fungi, namely *Fusarium oxysporum*, *Aspergillus niger* and *A. flavus* by the poison plate technique at a concentration of 100 μg/mL. Three kinds of fungi were incubated in potato dextrose agar (PDA) at 25±1 °C for 5 days to obtain new mycelium for the antifungal assay; then the mycelia as disks of approximately 0.45 cm diameter cut from the culture medium were picked up with a sterilized inoculation needle and inoculated in the centre of a PDA plate. The test compounds were dissolved in acetone (10 mL) and then added to the potato dextrose agar medium (PDA, 90 mL). The final concentration of the compounds in the medium was adjusted to 100 μg mL^{-1}. The inoculated plates were incubated at 25±1 °C for 5 days. Acetone was diluted with sterilized distilled water and used as the control, while clotrimazole (100 μg mL^{-1}) was used as the standard. For each treatment, three replicates of the experiments were performed. The radial growth of the fungal colonies was measured on the sixth day.

RESULTS AND DISCUSSION

The synthetic route for 6-[3-aryl-1-phenyl-4′,5′-dihydro[4,5′-bi-1*H*-pyrazol]-3′-yl]-2*H*-chromen-5-ols is illustrated in Schemes 1 and 2. The synthesis of title compounds involved the preliminary preparation of 1-(5-hydroxy-2*H*-chromen-6-yl)ethanone (**3**). Starting from resacetophenone (**1**) upon treating with propargyl bromide in the presence of anhydrous K_2CO_3 in dry acetone yielded 1-(2-hydroxy-4-(prop-2-yn-1-yloxy)phenyl)ethanone (**2**), which was further refluxed in *N*,*N*-dimethylaniline at 180 °C for 3 h to give compound **3**[27] (Scheme 1). Claisen–Schmidt condensation between 1-(5-hydroxy-2*H*-chromen-6-yl)ethanone (**3**) and substituted pyrazole aldehydes (**4a**–**j**) in the presence of powdered KOH under microwave irradiation for 4–7 min (Scheme 2) gave 3-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)-1-(5-hydroxy-2*H*-chromen-6-yl)prop-2-en-1-ones[27] **5a**–**j**. These chalcones were then cyclised by means of hydrazine hydrate and few drops of glacial acetic acid under conventional heating and microwave irradiation to furnish the title compounds **6a**–**j** in excellent yields.



Scheme 1. Synthesis of 1-(2-hydroxy-4-(prop-2-yn-1-yloxy)phenyl)ethanone (**3**).



Scheme 2. Synthesis of 6-[3-aryl-1-phenyl-4′,5′-dihydro[4,5′-bi-1*H*-pyrazol]-3′-yl]-2*H*-chromen-5-ols (**6a**–**j**).

Preliminarily, the synthesis of compounds **6a–j** was carried out under conventional heating method, but this method suffered from poor yields (57–62 %).

In order to improve the yields and reduce the reaction time, the synthesis approach was changed to the microwave irradiation method. Microwave-assisted synthesis of title compounds **6a–j** is advantageous over conventional method in terms of higher yields in shorter reaction times. A comparison of the yields of the title compounds prepared by the conventional and microwave irradiation methods is demonstrated in Table I.

TABLE I. Comparison of yields (isolated) of compounds **6a**–**j** under different synthetic conditions

Compound	Melting point, °C	Conventional		MWI	
		Time, h	Yield, %[a]	Time, min	Yield, %[a]
6a	98–100	2	61	1	95
6b	102–104	2	59	1	93
6c	101–103	2	60	1	94
6d	94–96	2	60	1	96
6e	104–106	2	58	2	86
6f	99–101	2	62	2	96
6g	108–110	1	62	1	96
6h	103–105	2	60	2	92
6i	90–92	2	60	2	90
6j	136–138	2	57	2	89

[a]Isolated yields

Formation of the 6-[3-aryl-1-phenyl-4′,5′-dihydro[4,5′-bi-1*H*-pyrazol]-3′-yl]--2*H*-chromen-5-ols (**6a–j**) were confirmed by IR, ^{1}H-NMR, ^{13}C-NMR, MS and elemental analyses. The IR spectrum of compound **6h** showed absorption bands at 3464, 3268 and 1596 cm^{-1} due to OH, NH and C=N groups, respectively. The ^{1}H-NMR spectrum of **6h** displayed two characteristic signals due to the diastereotopic protons (H_A, H_B). The H_A proton, which is *cis* to H_X resonated upfield at δ 3.09 ppm as a doublet of doublets (*dd*) with *J* values of 8.87 and 16.24 Hz, while the H_B proton which is *trans* to H_X resonated downfield at δ 3.48 ppm (*dd*) with *J* values 10.19, 16.24 Hz. The H_X proton which is vicinal to two methylene protons (H_A and H_B) was observed as doublet of doublets (*dd*) at δ 5.08 ppm with *J* values of of 8.87 and 10.19 Hz. A triplet appeared at δ 1.43 ppm was due to aliphatic CH_3 proton and quartet at δ 4.09 ppm due to Ar–O–CH_2. The NH proton appeared at δ 5.90 ppm as a broad singlet. The pyrazole proton appeared as a singlet at δ 7.98 ppm and a broad singlet was observed at δ 11.38 ppm due to the OH proton. In the ^{13}C-NMR spectrum of **6h**, CH_3, pyrazoline-CH_2, pyrazoline CH and Ar-OCH_2 carbons appeared at δ 14.8, 40.9, 54.1 and 63.5 ppm, respectively. The mass spectra of **6h** showed the molecular ion peak at *m*/*z* 479 $[M+H]^+$.

Antimicrobial activity

Antibacterial activity. The synthesized compounds were screened *in vitro* for antibacterial activity against different types of bacterial strains *viz*. Gram-positive bacterial strains *Staphylococcus aureus* (ATCC 9144) and *Bacillus subtilis* (ATCC 6633), and Gram-negative bacterial strains *Escherichia coli* (ATCC 25922) and *Proteus vulgaris* at concentrations of 10 and 20 μg mL^{-1}. The inhibitory efficiency of the synthesized compounds was measured through the zone of inhibition (in mm) compared with the standard drug gatifloxacin and the results are presented in Table II. The study of the antibacterial efficiency of the synthesized compounds revealed that most of the tested compounds displayed variable inhibitory effects on the growth of the tested Gram-positive and Gram--negative bacterial strains compared to the standard drug gatifloxacin at concentrations of 10 and 20 μg mL^{-1}. The compounds **6d** (Ar = 4-methylphenyl), **6e** (Ar = 4-hydroxyphenyl), **6f** (Ar = 4-methoxyphenyl) and **6i** (Ar = 3,4-dimethoxyphenyl) showed the equipotent activity through the zone of inhibition (Table II) against *S. aureus*, *B. subtilis*, *E. coli* and *P. vulgaris*, respectively. Compound **6e** exhibited the most potent antibacterial activity against Gram-positive and Gram--negative bacterial strains. The remaining compounds showed moderate activity compared to the standard. An analysis of the antibacterial activity results indicated that compound with electron-donating groups, such as methyl, hydroxy and methoxy, on the phenyl ring were more potent as compared to the control drug gatifloxacin.

TABLE II. Antimicrobial activity of synthesized compounds (zone of inhibition, mm)

Compound	Gram-positive bacteria				Gram-negative bacteria				Fungal strains		
	S. aureus		*B. subtilis*		*E. coli*		*P. vulgaris*		*A. flavus*	*A. niger*	*F. oxysporum*
6a	15[a]	26	12	22	12	19	09	12	13.3	13.6	13.9
6b	15	25	15	25	13	17	08	14	11.5	14.1	12.4
6c	13	23	14	21	10	16	09	11	**17.2**	**17.5**	**18.1**
6d	**19**	**31**	**18**	**35**	**16**	**23**	**10**	**17**	12.9	14.1	15.6
6e	**21**	**34**	**19**	**36**	**18**	**25**	**11**	**18**	08.7	13.4	15.3
6f	**20**	**32**	**18**	**33**	**16**	**23**	**11**	**17**	**16.9**	**15.2**	**17.7**
6g	17	28	16	30	16	20	10	16	15.1	14.7	16.1
6h	13	21	10	23	12	17	08	12	14.4	12.1	15.7
6i	**21**	**33**	**19**	**34**	**17**	**25**	**11**	**16**	**17.0**	**17.3**	**18.0**
6j	14	21	10	19	09	16	08	12	12.4	13.1	13.7
Gatifloxacin	21	33	20	36	18	25	12	18	–	–	–
Clotrimazole	–	–	–	–	–	–	–	–	17.3	17.7	18.4

Antifungal activity

The antifungal activity of the synthesized compounds was tested against three pathogenic fungi, *viz. Aspergillus flavus*, *A. niger* (ATCC 9029) and *Fusarium oxysporum* by the poison plate technique at a concentration of 100 μg mL^{-1}. Most of the synthesized compounds showed promising antifungal activity compared to standard drug clotrimazole (Table II). The compounds **6c**, **6f** and **6i** showed equipotent inhibition compared to the standard drug against the tested fungi, whereas the remaining compounds showed moderate activity against the pathogenic fungi.

CONCLUSION

In summary, a new series of compounds **6a**–**j** was synthesized under conventional and microwave irradiation conditions. Using the microwave irradiation method, the reactions were completed in short reaction times under mild reaction conditions, in high yields and convenient operation. All the titled compounds were screened for their *in vitro* antimicrobial activity. Compound **6e** was found to be the most potent and compounds **6d**, **6f** and **6i** were found to be equipotent compared to the standard drug gatifloxacin against the pathogenic bacteria whereas compounds **6c**, **6f** and **6i** exhibited potent activity against the pathogenic fungi compared to the standard drug clotrimazole at their respective concentrations. The antifungal screening results revealed that compounds **6f** and **6i** could be considered as promising antifungal drug candidates.

SUPPLEMENTARY MATERIAL

Spectral and analytical data of the synthesized compounds are available electronically at the pages of journal website: http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

Acknowledgement. The authors are thankful to The Head of Department of Chemistry, Osmania University, for providing laboratory facilities and the Director of Central Facilities for Research and Development (CFRD), Osmania University, for providing IR and NMR spectral analysis. Financial support from UGC, New Delhi, India, for RK is gratefully acknowledged.

ИЗВОД

СИНТЕЗА УПОТРЕБОМ МИКРОТАЛАСА И ИСПИТИВАЊЕ АНТИМИКРОБНЕ АКТИВНОСТИ СЕРИЈЕ 6-[3-АРИЛ-1-ФЕНИЛ-[4,5′-БИ-1*H*-ПИРАЗОЛ]-3′-ИЛ]ДИХИДРО-2*H*-ХРОМЕН-5-ОЛА

DONGAMANTI ASHOK[1], RANGU KAVITHA[1], SRINIVAS GUNDU[1] и MADDERLA SARASIJA[2]

[1]*Green and Medicinal Chemistry Laboratory, Department of Chemistry, Osmania University, Hyderabad 500 007, India* и [2]*Department of Chemistry, Satavahana University, Karimnagar-505001, India*

Синтетисана је серија деривата 6-[3-арил-1-фенил-[4,5′-би-1*H*-пиразол]-3′-ил]дихидро-2*H*-хромен-5-ола применом реакције Мајклове адиције чалкона (**5a**–**j**) и хидразин-хидрата уз присуство натријум-ацетата, под условима традиционалног загревања и применом микроталасног зрачења. Структура добијених једињења одређена је на основу IR, ^{1}H-NMR, ^{13}C-NMR, MS и аналитичких података. Испитана је антимикробна активност свих синтетисаних једињења **6a**–**j** према различитим сојевима бактерија и гљива. Већина једињења показује антимикробну активност, а једињења **6c**–**f** и **6i** показују велики антимикробни потенцијал.

(Примљено 6. децембра 2017, ревидирано 7. децембра, прихваћено 21. децембра 2018)

REFERENCES

1. K. Chrag, C. S. Patel, B. Rami, C. N. Panigrahi, *J. Chem. Pharm. Res.* **2** (2010) 73

2. D. V. Dekhane, S. S. Pawar, S. Gupta, M. S. Shingare, C. R. Patil, S. N. Thore, *Bioorg. Med. Chem. Lett.* **21** (2011) 6527
3. C. Y. Zhang, X. H. Liu, B. L. Wang, S. H. Wang, Z. M. Li, *Chem. Biol. Drug Design* **75** (2010) 489
4. Z. Yuhan, X. Na, W. Guowei, Q. Jingping, *J. Chem. Res*. **34** (2014) 684
5. B. L. Finkelstein, C. J. Strock, *Pest. Sci*. **50** (1997) 324
6. S. A. F. Rostom, M. A. Shalaby, M. A. El-Demellawy, *Eur. J. Med. Chem*. **38** (2003) 959
7. O. I. El-Sabbagh, M. M. Baraka, S. M. Ibrahim, C. Pannecouque, G. Andrei, R. Snoeck, J. Balzarini, A. A. Rashad, *Eur. J. Med. Chem*. **44** (2009) 3746
8. D. Kaushik, S. A. Khan, G. Chawla, S. Kumar, *Eur. J. Med. Chem.* **45** (2010) 3943
9. A. Balbi, M. Anzaldi, C. Macciò, C. Aiello, M. Mazzei, R. Gangemi, P. Castagnola, M. Miele, C. Rosano, M. Viale, *Eur. J. Med. Chem.* **46** (2011) 5293
10. R. R. Ranatunge, D. S. Garvey, D. R. Janero, L. G. Letts, A. M. Martino, M. G. Murty, S. K. Richardson, D. V. Young, I. S. Zemetseva, *Bioorg. Med. Chem.* **12 (**2004) 1357
11. T. M. Fong, S. B. Heymsfield, *Int. J. Obes.* **33** (2009) 947
12. S. M. Sakya, H. Cheng, K. M. Lundy DeMello, A. Shavnya, M. L. Minich, B. Rast, J. Dutra, C. Li, R. J. Rafka, D. A. Koss, J. Li, B. H. Jaynes, C. B. Ziegler, D. W. Mann, C. F. Petras, S. B. Seibel, A. M. Silvia, D. M. George, A. Hickman, M. L. Haven, M. P. Lynch, *Bioorg. Med. Chem. Lett.* **16** (2006) 1202
13. M. I. Husain, S. Shukla, *Indian J. Chem*., *B* **25** (1986) 983
14. V. H. Babu, C. H. Sridevi, A. Joseph, K. K. Srinivasan, *Ind. J. Pharm. Sci.* **69** (2007) 470
15. F. F. Barsoum, H. M. Hosni, A. S. Girgis, *Bioorg. Med. Chem.* **14** (2006) 3929
16. Y. K. Agrawal, K. Manna, V. H. Babu, K. K. Srinivasan, H. Bhatt, P. J. Gogoi, *Indian J. Heterocycl. Chem.***16** (2007) 263
17. M. Abid, A. Azam, *Eur. J. Med. Chem.* **40** (2005) 935
18. M. Amir, H. Kumar, S. A. Khan, *Bioorg. Med. Chem. Lett.* **18** (2008) 918
19. A. M. Fahmy, K. M. Hassa, A. A. Khalaf, R. A. Ahmed, *Indian J. Chem.* **26** (1987) 884
20. R. A. Nugent, M. Murphy, S. T. Schlachter, C. J. Dunn Smith R. J. Staite L. A. Galinet, S. K. Shields, D. G. Aspar, K. A. Richard, N. A. Rohloff, *J. Med. Chem.* **36** (1993) 134
21. S. Rich, J. G. Horsfall, *CA* **46** (1952) 11543
22. H. Kawazura, Y. Takahashi, Y. Shinga, F. Shimanda, N. Ohto, A. Tamura, *Jpn. J. Pharmacol*. **73** (1997) 317
23. E. Palaska, M. Aytemir, T. Uzbay, D. Erol, *Eur. J. Med. Chem.* **36** (2001) 539
24. S. A. Wadhal, K. N. Wadokar, P. S. Pande, *Indian J. Heterocycl. Chem.* **15** (2005) 11
25. E. L. Anderson, J. E. Casey, L. C. Greene, J. J. Lafferty, H. E. Reiff, *J. Med. Chem.* **7** (1984) 25
26. H. J. Benson, *Microbiological applications*, 5th ed, W. C. Brown Publications, Boston, MA, 1990.
27. P. Sreenivas, *Indian J. Chem., Sect. B* **50** (2011) 1484
28. D. Ashok, K. Rangu, V. Hanumantha Rao, S. Gundu, B. Srilata, M. Vijjulatha, *Med. Chem. Res.* **25** (2016) 501.