International Research Journal of Natural and Applied Sciences
ISSN: (2349-4077)
Impact Factor- 5.46, Volume 4, Issue 11, November 2017
Website- www.aarf.asia, **Email** : editor@aarf.asia , editoraarf@gmail.com

SYNTHESIS OF 1-SUBSTITUTED-2-[2-(4, 5/5, 6/5, 7-DIMETHYL)-2-OXOINDOLIN-3-YLIDENE) HYDRAZINYL]-3-PHENYLQUINAZOLIN-4(*3H*) ONES AS ANTIFUNGAL AGENTS

Nisheeth Rastogi[1]*, Darwin Anil Harrison[1] and Masihur Rahman[2]

[1]Dr. W. E. Bauer Research Laboratory, Department of Chemistry, Lucknow Christian Post-Graduate College, Lucknow-226018 (U.P.), India

[2]Department of Chemistry, Integral University, Lucknow-226026 (U.P.), India

ABSTRACT

*Some new 1-substituted-2-[2-(4, 5/5, 6/5, 7-dimethyl)-2-oxoindolin-3-ylidene) hydrazinyl]-3-phenylquinazolin-4(3H) ones (**3-17**) have been prepared by the reaction of 2-hydrazinyl-3-phenylquinazolin-4(3H)-one and 1-substituted 4,5/5,6/5,7-dimethylindolin-2,3-diones. Structures of the compounds have been elucidated with the help of elemental analysis and spectral data (IR, ^{1}H-NMR and Mass). Compounds have also been screened for their antifungal potential against human pathogenic fungi.*

Introduction

Quinazolinone is a bicyclic compound consisting of a pyrimidine system fused at 5,6-position with benzene ring, has a broad spectrum of biological activities such as antitubercular[1], antimicrobial[2], CNS depressant[3], anticonvulsant[4], cytotoxic[5], analgesic, antiinflammatory[6], antitumor[7]and antiamnestic[8]. Similarly indolin-2,3-diones and their derivatives possess anthelmintic[9], antiinflammatory[10], analgesic[11], antimalarial[12], antioxidant[13], anti-epileptic[14], anticonvulsant[15], antitubercular[16], cytotoxic[17], antimicrobial[18], antifertility[19], CNS depressant[20]

and enzyme inhibitory[21]. Keepimg biological activity of quinazolinone derivatives and indolin-2,3-diones in mind it was considered worthwhile to condense both the nuclei in a single molecule and screen them for antigungal potential.

2-Mercapto-3-phenylquinazolin-4(*3H*)-one **(1)**[22] on hydrazinolysis with hydrazine hydrate gave 2- hydrazinyl-3-phenylquinazolin-4(*3H*)-one **(2)** which in turn was obtained by the reaction of 2-aminobenzoic acid with phenylisothiocyanate. 2- Hydrazinyl-3-phenylquinazolin-4(*3H*)-one **(2)** on condensation with 1- substituted 4,5/5,6/5,7-dimethylindolin-2,3-diones gave 1-substituted-2-[2-(4, 5/5, 6/5, 7-dimethyl)-2-oxoindolin-3-ylidene) hydrazinyl]-3-phenylquinazolin-4(*3H*) ones (**3-17**). 4, 5 and 5, 6-dimethylindolin-2,3-diones were synthesised by the reaction of 3,4-dimethylaniline with chloral hydrate and hydroxylamine hydrochloride to get isonitrosoacetanilide intermediate which on cyclization with concentrated sulfuric acid gave a mixture of 4, 5-and 5, 6- dimethylindolin-2,3-diones while 5,7-dimethylindolin-2,3-dione was obtained by using 2,4-dimethylaniline. 4,5 and 5, 6- dimethylindolin-2,3-diones were separated using the method of Varma and Singh[23]. 1-methyl, ethyl, acetyl and benzyl 4, 5/5, 6/5, 7-dimethylindolin-2, 3-diones were prepared by the reaction of the respective isatins with dimethyl sulphate, ethyl bromide, acetic anhydride and benzyl bromide.

Antifungal activity

Compounds **3-17** were screened for their *in-vitro* antifungal potential against human pathogenic fungi viz: *Candida albicans* (CA), *Cryptococcus neoformans* (CN), *Candida parapsilosis* (CP), *Trichophyton mentagrophytes* (TM) and *Aspergillus fumigatus* (AF) using tube dilution method at a maximum concentration of 100μg/mL in DMSO and Minimum Inhibitory Concentration (MIC) values were determined in μg/mL. Fluconazole was taken as standard drug. Antifungal activity data are shown in Table-1. All the compounds were found to be inactive against *Cryptococcus neoformans* but found to be quite active against *Trichophyton mentagrophytes* and *Aspergillus fumigatus* and a common trend was observed against *Trichophyton mentagrophytes* and *Aspergillus fumigatus.* No clear cut Structure Activity Relationship could be established.

Table-1 Minimum Inhibitory Concentration MIC (µg/mL) of compounds against fungi

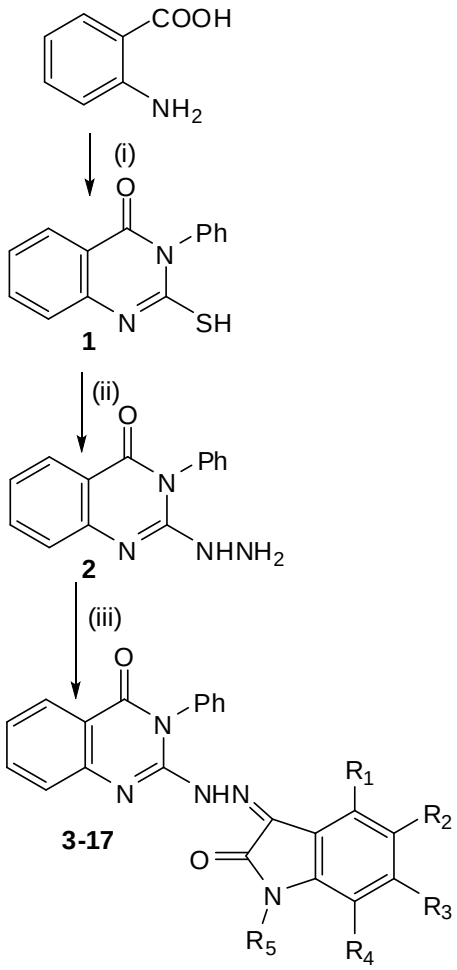
Compd	CA	CN	CP	TM	AF
1	>100	>100	50	3.12	6.25
2	12.5	>100	50	3.12	3.12
3	12.5	>100	>100	3.12	3.12
4	25	>100	>100	6.25	6.25
5	12.5	>100	>100	3.12	3.12
6	12.5	>100	25	6.25	3.12
7	>100	>100	25	6.25	6.25
8	12.5	>100	25	3.12	3.12
9	12.5	>100	>100	6.25	3.12
10	>100	>100	>100	6.25	6.25
11	12.5	>100	>100	3.12	3.12
12	12.5	>100	6.25	6.25	3.12
13	>100	>100	50	6.25	6.25
14	12.5	>100	50	3.12	3.12
15	12.5	>100	12.5	6.25	3.12
Fluconazole (Standarddrug)	0.5	1.0	2.0	1.0	2.0

Experimental

The melting points were determined in open capillary tubes in sulphuric acid bath and are uncorrected. IR spectra were recorded in KBr on a Perkin Elmer spectrophotometer and frequencies are presented as cm-^{1}. ^{1}H-NMR spectra were recorded on Bruker Avance 300 spectrometer using DMSO-d_6 as solvent and TMS as internal reference. Chemical shifts are expressed in δ (ppm). Mass spectra were recorded on Jeol-JMS-300 spectrometer. Elemental analysis data were obtained on Carlo Erba 1108 analyser. Homogeneity of the compounds was checked on TLC silica gel G plates and spots were located by exposure to iodine vapours. Physical data of the compounds prepared are shown in table-2.

1-Substituted-2-[2-(4, 5/5, 6/5, 7-dimethyl)-2-oxoindolin-3-ylidene) hydrazinyl]-3-phenylquinazolin-4(*3H*) ones 3-17 (General method)

A mixture of 2-hydrazinyl-3-phenylquibazolin-4(*3H*)one **(2)** (5 mmol) and 1-substituted-4, 5/5, 6/5, 7-dimethylindolin-2,3-diones (5 mmol) in ethanol (70 mL) containing 2-3 drops of glacial acetic acid was refluxed for 2-3h and left over night at room temperature. The solid thus obtained was filtered, washed with methanol and recrystallised from aq. DMF.



(i) PhNCS (ii) $N_2H_4.H_2O$, EtOH (iii) 1-Substituted-4,5/5,6/6,7-dimethylindolin-2,3-diones, EtOH, gl. AcOH

R_1, R_2, R_3, R_4, = H, Me; R_5=H, Me, Et, Ac, Bz

SCHEME-1

Spectral data of some of compounds prepared

(3) IR (KBr) cm-^{1}: 3413, 3381 (NH), 1725, 1691 (CO); **^{1}H-NMR (300MHz, DMSO-d_6) δppm:** 2.12, 2.33 (s, 6H, 2 x Me), 4.35 (s, 1H, NH), 6.89-8.05 (m, 6H, Ar-H), 12.43 (s, 1H, NH); **MS m/z:** 356 (M^+). **(9) IR (KBr) cm-^{1}:** 3410 (NH), 1715, 1687 (CO)); **^{1}H-NMR (300MHz, DMSO-d_6) δppm:** 2.20 (s, 6H, 2 x Me), 2.63 (s, 3H, NMe), 4.33 (s, 1H, NH), 6.89-8.05 (m, 6H, Ar-H); **MS m/z:** 423. **(10) IR (KBr) cm-^{1}:** 3411 (NH), 1729, 1689 (CO); **^{1}H-NMR (300MHz, DMSO-d_6) δppm:** 2.15- 2.36 (t, 3H, Me), 2.56-2.67 (q, 2H, CH_2Me), 3.20 (s, 2H, 2 x Me), 4.35 (s, 1H, NH), 6.89-8.05 (m, 6H, Ar-H); **MS m/z:** 437 (M^+). **(16) IR (KBr) cm-^{1}:** 3417 (NH), 1725, 1713, 1695 (CO); **^{1}H-NMR (300MHz, DMSO-d_6) δppm:** 2.32 (s, 3H, COMe), 2.67, 3.10 (s, 6H, 2 x Me), 4.35 (s, 1H, NH), 6.89-8.05 (m, 6H, Ar-H); **MS m/z:** 451 (M^+). **(17) IR (KBr) cm-^{1}:** 3418 (NH), 1720, 1700 (CO); **^{1}H-NMR (300MHz, DMSO-d_6) δppm:** 2.67. 3.10 (s, 6H, 2 x Me), 3.13 (s, 2H, CH_2Ph), 4.35 (s, 1H, NH), 6.89-8.05 (m, 6H, Ar-H); **MS m/z:** 499 (M^+).

Table-2 Characterization data of compounds prepared

Compd	R_1	R_2	R_3	R_4	R_5	M.P. (^{o}C)	Yield %	Elemental analysis %			Moleular formula
								C	H	N	
								Found (Calcd)			
3	Me	Me	H	H	H	>250	67	70.34 (70.40)	4.63 (4.68)	17.02 (17.10)	$C_{24}H_{19}N_5O_2$
4	Me	Me	H	H	Me	>250	78	70.87 (70.91)	4.89 (5.00)	16.50 (16.54)	$C_{25}H_{21}N_5O_2$
5	Me	Me	H	H	Et	>250	78	71.30 (71.38)	5.26 (5.30)	15.89 (16.01)	$C_{26}H_{23}N_5O_2$
6	Me	Me	H	H	Ac	>250	60	69.06 (69.17)	4.60 (4.69)	15.45 (15.51)	$C_{26}H_{21}N_5O_3$
7	Me	Me	H	H	Bz	>250	56	74.46 (74.53)	4.88 (5.05)	13.96 (14.02)	$C_{31}H_{25}N_5O_2$
8	H	Me	Me	H	H	>250	78	70.32 (70.40)	4.63 (4.68)	17.03 (17.10)	$C_{24}H_{19}N_5O_2$

9	H	Me	Me	H	Me	>250	78	70.84 (70.91)	4.88 (5.00)	16.46 (16.54)	$C_{25}H_{21}N_5O_2$
10	H	Me	Me	H	Et	>250	77	71.31 (71.38)	5.19 (5.30)	15.89 (16.01)	$C_{26}H_{23}N_5O_2$
11	H	Me	Me	H	Ac	>250	70	69.06 (69.17)	4.63 (4.69)	15.46 (15.51)	$C_{26}H_{21}N_5O_3$
12	H	Me	Me	H	Bz	>250	67	74.50 (74.53)	4.97 (5.05)	13.98 (14.02)	$C_{31}H_{25}N_5O_2$
13	H	Me	H	Me	H	>250	80	70.43 (70.40)	4.58 (4.68)	17.05 (17.10)	$C_{24}H_{19}N_5O_2$
14	H	Me	H	Me	Me	>250	78	70.89 (70.91)	4.88 (5.00)	16.50 (16.54)	$C_{25}H_{21}N_5O_2$
15	H	Me	H	Me	Et	>250	78	71.32 (71.38)	5.20 (5.30)	15.87 (16.01)	$C_{26}H_{23}N_5O_2$
16	H	Me	H	Me	Ac	>250	76	69.07 (69.17)	4.63 (4.69)	15.46 (15.51)	$C_{26}H_{21}N_5O_3$
17	H	Me	H	Me	Bz	>250	70	74.45 (74.53)	4.88 (5.05)	13.89 (14.02)	$C_{31}H_{25}N_5O_2$

Acknowledgemant

Authors are thankful to the Manager and Principal, LCPGC, for providing laboratory facilities and encouragement and the Head, SAIF, CDRI, Lucknow for IR and ^{1}H-NMR data.

References

1. A. O. Al-Deeb and A. M. Alafeefy, *World Appl. Sci. J*. 2008, **5**, 94.
2. (a) N. B. Patel, F. M. Shaikh, V. N. Patel, H. R. Patel and J. C. Patel, *Int. J. Drug Design Dis*., 2010, **1**, 212; (b) A. K. Tiwari, V. K. Singh, A. Bajpai, G. Shukla, S. Singh and A. K. Mishra, *Eur. J. Med. Chem*., 2007, **42**, 1234.
3. V. Jatav, P. Mishra, S. Keshav and J. P. Stables, *Eur. J. Med. Chem*., 2008, **43**, 135.

4. A. Gupta, S. K. Keshaw, N. Jain, H. Rajak, A. Soni and J. P. Stables, *Med. Chem. Res*., 2011, **20**, 1638; (b) P. Hangovan, S. Ganguly, V. Pandi and J. P. Stables, *Der Pharmacia Lett*., 2010, **2**, 13.
5. D. Raffa, M. C. Edler, G. Daidone, B. Maggio, M. Merickech, S. Plescia, D. Schillaci, R. Bai and E. Hamel, *Eur. J. Med. Chem*., 2004, **39**, 299.
6. (a) K.Hemalatha and K. Girija, *Int. J. Pharm. Pharm. Sci*., 2011, 103; (b) M. S. Mohamed, M. M. Kamel, E. M. Kassem, N. Abotalab, S. M. Nofal anf M. F. Ahmad, *Acta Poloniae Pharm. Drug Res*., 2009, **66**, 487.
7. V. Alagarsamy,d M. R. Yadav, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1877.
8. S. Kovalenko, L. Belenichev, V. Vikitin and A. Karpenko, *Acta Poloniae Pharm. Drug Res.*, 2003, **60**, 275.
9. B. D. Prasad, B. C. Kanth, D. Prabhakar, K. P. Kumar and V.G. Sastry, *Int. J. Pharmacy Therapeutics*, 2012, **3**, 78.
10. (a) K. Swathi and M. Sarangapani, *World J. Pharm. Pharm. Sci.*, 2014, **3**, 2070 ; (b) S. M. Kumar, D. S. Kumar, S. Kumargupta, S. P. Pandey and R. Yadav, *Asian J. Pharm. Res.*, 2011, **1**, 62.
11. S. Suresh, K. B. Priyanka, P. Maharaj, Ch. Srikanth, K. Karthik and G. Sammaiah, *Asian J. Pharm. Clin. Res.*, 2013, **1**, 65.
12. S. C. Shingade, S. B. Bari, P. Agarwal and K. Srivastava, *Indian J. Chem.*, Sect. B, 2013, **52**, 1236.
13. K. Karthik, K. B. Priyanka, S. Manjula and G. Sammaiah, *Int. J. Pharm. Pharm. Sci.*, 2013, **5**, 224.
14. C. R. Prakash, S. Raja and G. Saravanan, *Int. J. Pharm. Pharm. Sci.*, 2014, **6**, 539.
15. (a) M. Rahmani-Khajouei, A. Mohammadi-Farani, D. Mirzaei and A. Aliabadi, *J. Reports Pharm. Sci.*, 2017, **6**, 13; (b) M. Divar, Y. Yeganeh, A. Jamshidzadeh, R. Heidari and S.Khabnadideh, *J. Innov. Appl. Pharm. Sci*, 2017, 2, 4.
16. T. Aboul-Fadl and F. A. S. Bin-Jubair, *Int. J. Res. Pharm*., 2010, **1**, 113.
17. (a) A. T. Taher, N. A. Khalil and E. M. Ahmed, *Arch. Pharm. Res*., 2011, **4**, 1615; (b) S. S. Reddy, R. Pallela, D-M Kim, M-S Won, and Y-B Shim, *Chem. Pharm. Bull*., 2013, **61**, 1105; **(c)** A. El-Faham, M. Farooq, S. N. Khattab, N. Abutaha, M. A. Wadaan, H. A. Ghabbour and H-K Fun, *Molecules* 2015, **20**, 14638; doi:10.3390/molecules200814638.

18. (a) H. Ramadoss, D. Saravanan, S. P. N. Sudhan and S.S. Mansoor, *Der Pharma Chemica*, 2016, **8**, 94; (b) P. S. Bhasin, N. Sachdeva, S. N. Pandeya, G. Nath and S.K. Singh, *Acta Pharm. Turcica*, 2005, **47**, 21; (c) A. V. Bogdanov, A. M. Vazykhova, N. R. Khasiyatullina, D. B. Krivolapov, A. B. Dobrynin, A. D. Voloshina, V. F. Mironov, *Chem. Heterocyclic Comp*., 2016, **52**, 25.
19. K. C. Joshi, R. Jain, P. Chand and S. Garg, *J. Indian Chem. Soc.*, 1983, **60**, 760.
20. V. Raj, *Int. J. Curr. Pharm. Res*., 2012, **4**, 1.
21. S. Noshi, K. Zaigham, K. A. Shahzad and T. M. Rana, *Biomed. Lett.*, 2016, **2**, 49.
22. A. Amir, I. Ali and M. Z. Hussan, Indian J. Chem., Sect B, 2014, **53**, 597.
23. R. S. Varma and A. P. Singh, *Indian J. Chem*., Sect.B, 1990, **29**, 578