Journal of Enzyme Inhibition and Medicinal Chemistry, April 2009; 24(2): 480–486

Design, synthesis, characterization and *in vitro* antimicrobial evaluation of 4,6-diaryl-4,5-dihydro-2-phenyl-2*H*-indazol-3-ols

M. GOPALAKRISHNAN†, J. THANUSU, & V. KANAGARAJAN

Synthetic Organic Chemistry Laboratory, Department of Chemistry, Annamalai University, Annamalainagar-608 002, Tamil Nadu, India

(*Received 14 February 2008; accepted 20 April 2008*)

Abstract

New 4,6-diaryl-4,5-dihydro-2-phenyl-2*H*-indazol-3-ols **25-32** were designed, synthesized and *in vitro* microbially evaluated using clinically isolated bacterial strains viz *Staphylococcus aureus, β-Heamolytic streptococcus, Vibreo cholerae, Salmonella typhii, Shigella felxneri* and fungal strains viz *Aspergillus flavus, Mucor, Rhizopus* and *Microsporum gypsuem*. Results of this study showed that the nature of the substituents on the phenyl rings *viz*., methyl, methoxy, chloro, nitro as well as the bromo functions at the *meta* and *para* positions of the aryl moieties determined the nature and extent of the activity of the fused indazolonol compounds **25-32**.

Keywords: *6-Carbethoxy-3, 5-diarylcyclohex-2-enone, 4,6-Diaryl-4,5-dihydro-2-phenyl-2*H*-indazol-3-ols, Phenyl hydrazine hydrochloride, Antibacterial activity, Antifungal activity*

Introduction

In recent years there has been a great deal of interest in exploiting more than one proximal functional groups for designing novel structures capable of performing a variety of functions. The present study describes the use of 6-carbethoxy-3,5-diarylcyclohex-2-enone [1], an intermediate with three versatile functional groups i.e., ketone, olefin and ester for the synthesis of fused indazole derivatives.

A variety of structurally diverse indazole nucleus have aroused great interest in the past and recent years due to their wide variety of biological properties such as antimicrobial activity [2], inhibitors of protein kinase B/Akt [3], antiprotozoal agents [4], antichagasic activity [4], leishmanocidal activity [4], trypanocidal activity [4], inhibitors of S-adenosyl homocysteine/methylthio adenosine (SAH/MTA) nucleosides [5], potent activator of the nitric oxide receptor [6] and inhibition of platelet aggregation [6].

In continuation of our earlier work on the synthesis of various bio active heterocyclic nuclei including biolabile piperidone, 1,2,3-selenadiazoles, 1,2,3-thiadiazoles, 1,2,4,5-tetrazinanes [7–11], we wish to report the development of fused indazoles on 6-carbethoxy-3, 5-diarylcyclohex-2-enone derivatives thus paving the way for a novel class of 4,6-diaryl-4,5-dihydro-2-phenyl-2*H*-indazol-3-ol.

Experimental

Microbiology

Materials. All the bacterial strains namely Staphylococcus aureus, β-Heamolytic streptococcus, Vibreo cholerae, Salmonella typhii and Shigella felxneri and fungal strains namely Aspergillus flavus, Mucor, Rhizopus and Microsporum gypsuem were clinically isolated strains and were obtained from Faculty of Medicine, Annamalai University, Annamalainagar-608 002, Tamil Nadu, India.

Correspondence: M. Gopalakrishnan, Synthetic Organic Chemistry Laboratory, Department of Chemistry, Annamalai University, Annamalai University, 608 002, Tamil Nadu, India. Tel.: + 91 4144 228 233, E-mail: profmgk@yahoo.co.in

ISSN 1475-6366 print/ISSN 1475-6374 online © 2009 Informa UK Ltd.
DOI: 10.1080/14756360802218078

In vitro antibacterial and antifungal activity (Minimum Inhibitory Concentration (MIC) method). Minimum inhibitory concentration (MIC) in μg/mL values was carried out by two-fold serial dilution method [12]. The test compounds **23-27** were dissolved in water to obtain 1 mg mL^{-1} stock solution. Seeded broth (broth containing microbial spores) was prepared in nutrient broth (NB) from 24 h old bacterial cultures on nutrient agar (Hi-media, Mumbai) at 37 ± 1°C while fungal spores from 1 to 7 days old Sabourauds agar (Hi-media, Mumbai) slant cultures were suspended in sabourauds dextrose broth (SDB). The colony forming units (cfu) of the seeded broth were determined by plating technique and adjusted in the range of 10^4–10^5 cfu/mL. The final inoculums size was 10^5cfu/mL for antibacterial assay and 1.1–1.5 × 10^2 cfu/mL for antifungal assay. Testing was performed at pH 7.4 ± 0.2 for bacteria (NB) and at a pH 5.6 for fungi (SDB). Exactly 0.4 mL of the solution of test compound was added to 1.6 mL of seeded broth to form the first dilution. One milliliter of this was diluted with a further 1 mL of seeded broth to give the second dilution and so on till six such dilutions were obtained. A set of assay tubes containing only seeded broth was kept as control. The tubes were incubated in biological oxygen demand (BOD) incubators at 37 ± 1°C for bacteria and 28 ± 1°C for fungi. The minimum inhibitory concentrations (MICs) were recorded by visual observations after 24 h (for bacteria) and 72–96 h (for fungi) of incubation. Ciprofloxacin was used as standard for bacteria studies and Fluconazole was used as standards for fungal studies.

Chemistry

Performing TLC assessed the reactions and the purity of the products. All the reported melting points were taken in open capillaries and were uncorrected. IR spectra were recorded in KBr (pellet forms) on a Nicolet-Avatar–330 FT-IR spectrophotometer and noteworthy absorption values (cm^{-1}) alone are listed. ^{1}H, D_2O exchanged ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz respectively on Bruker AMX 400 NMR spectrometer using DMSO-*d* as solvent. Two-dimensional HSQC spectra were recorded at 500 MHz and on Bruker DRX 500 NMR spectrometer using DMSO-*d* as solvent. The ESI + ve MS spectra were recorded on a Bruker Daltonics LC-MS spectrometer. Satisfactory microanalysis was obtained on Carlo Erba 1106 CHN analyzer.

By adopting the literature procedure, 1,3-diaryl-prop-2-en-1-ones **9-16** [13–15] and 6-carbethoxy-3,5-diarylcyclohex-2-enone **17-24** [1] were prepared.

Typical procedure for the synthesis of 4,6-diphenyl-4,5-dihydro-2-phenyl-2H-indazol-3-ol ***25***. A solution of 6-carbethoxy-3,5-diphenylcyclohex-2-enone, **17** (0.1 mol) in methanol (40 mL) was treated with phenyl hydrazine hydrochloride (0.15 mol) and anhydrous sodium acetate (0.15 mol) and refluxed for 7 h. The reaction mixture was cooled and then poured over crushed ice. The crude product **25** was recrystallized twice using methanol as solvent. IR (KBr) (cm^{-1}): 3425, 3062, 2921, 2862, 1605, 1514, 1445, 1367, 757, 705, 695; ^{1}H NMR (δ ppm): 2.98–3.13, 3.46–3.50 (m,2H,H_5), 4.34 (dd,1H,H_4, J = 12.0,9.2 Hz), 6.86 (d,1H,H_7, J = 7.9 Hz), 7.20–7.58 (m,15H,H-Arom.), 11.73 (s,1H,OH); ^{13}C NMR (δ ppm): 34.4 C-4, 37.2 C-5, 99.2 C-9, 114.5 C-7; 136.6 C-8; 125.6–128.6 C-Arom.; 140.4, 142.2, 145.4 *ipso*-C's; 159.2 C-3.

In the D_2O exchanged ^{1}H NMR spectrum, a broad peak at 11.73 ppm due to —OH proton at C-3 was disappeared.

In the HSQC spectrum, one bond correlation (34.4/4.34) between C-4 and H_{4a} occurs. The ^{13}C resonance at 37.2 ppm has correlations with methylene protons H_{5a} (37.2/2.98–3.13; 36.2/3.46–3.50) and hence C-5 resonates at 37.2 ppm. The ^{13}C resonance at 114.5 ppm correlates with doublet at 6.86 ppm. The doublet at 6.86 ppm is conveniently assigned to H_7. The cross peak (114.5/6.86 ppm) confirms that the ^{13}C resonance at 114.5 ppm is due to C-7. The ^{13}C resonances at 99.2, 136.6, 159.2 ppm have no correlations with protons and hence it is due to quaternary carbons. Among the quaternary carbon resonances, the ^{13}C resonance at 140.4, 142.2, 145.4 ppm are assigned to *ipso* carbons. The ^{13}C resonance at 136.6 and 159.2 ppm are due to the C-8 and C-3 carbons. The signal at 99.2 ppm is due to C-9 carbon and the C-6 carbon is merged with aromatic carbons.

Compounds **26-32** were synthesized similarly.

4,5-Dihydro-2,6-diphenyl-4-p-tolyl-2H-indazol-3-ol. **26** IR (KBr) (cm^{-1}): 3419, 3062, 3065, 2917, 2857, 1592, 1514, 755, 708, 694; ^{1}H NMR (δ ppm): 2.34 (s,3H,CH_3 at phenyl ring); 2.95–3.10, 3.33–3.69 (m,2H,H_5), 4.01 (dd,1H,H_4, J = 12.4,9.6 Hz), 6.87 (d,1H,H_7, J = 8.5 Hz), 7.02–7.57 (m,14H,H-Arom.), 11.35 (s,1H,OH); ^{13}C NMR (δ ppm): 21.9 CH_3 at phenyl ring; 33.9 C-4, 37.3 C-5, 99.1 C-9, 114.5 C-7; 136.3 C-8; 125.3–128.6 C-Arom.; 140.2, 141.3, 142.3 *ipso*-C's; 159.4 C-3.

4-(4-chlorophenyl)-4,5-dihydro-2,6-diphenyl-2H-indazol-3ol. **27** IR (KBr) (cm^{-1}): 3404, 3053, 2926, 1602, 1534, 1492, 756, 711, 695; ^{1}H NMR (δ ppm): 2.95–3.10, 3.26–3.40 (m,2H,H_5), 4.35 (dd,1H,H_4, J = 13.1,8.7 Hz), 6.87 (d,1H,H_7, J = 8.0 Hz), 7.26–7.67 (m,14H,H-Arom.), 11.6 (s,1H,OH); ^{13}C NMR (δ ppm): 34.5 C-4, 37.4 C-5, 99.3 C-9, 114.7 C-7; 136.2 C-8; 125.1–128.8 C-Arom.; 140.1, 141.2, 142.4, 144.2 *ipso*-C's; 159.3 C-3.

4,5-dihydro-4-(4-nitrophenyl)-2,6-diphenyl-2H-indazol-3-ol. **28** IR (KBr) (cm^{-1}): 3421, 3075, 2922, 2846,

1597, 1515, 1433, 1346, 752, 708, 693; ^{1}H NMR (δ ppm): 2.96–3.29, 3.40–3.55 (m,2H,H_5), 4.44 (dd,1H,H_4, J = 12.6,8.4 Hz), 6.90 (d,1H,H_7, J = 8.2 Hz), 7.35–7.56 (m,14H,H-Arom.), 11.70 (s,1H,OH); ^{13}C NMR (δ ppm): 34.8 C-4, 37.2 C-5, 99.2 C-9, 114.3 C-7; 136.2 C-8; 123.4-128.8 C-Arom.; 140.1, 142.4, 146.2 *ipso*-C's; 159.2 C-3.

4,5-dihydro-4-(4-methoxyphenyl)-2,6-diphenyl-2H-indazol-3-ol. **29** IR (KBr) (cm^{-1}): 3416, 3064, 3051, 2932, 2835, 1606, 1511, 1441, 1372, 759, 712, 693; ^{1}H NMR (δ ppm): 2.94–3.20, 3.22–3.46 (m,2H,H_5), 3.85 (s,3H,OCH_3 at phenyl ring), 4.27 (dd,1H,H_4, J = 11.4,9.1 Hz), 6.85 (d,1H,H_7, J = 8.6 Hz), 7.12–7.55 (m,14H,H-Arom.), 11.40 (s,1H,OH); ^{13}C NMR (δ ppm): 34.8 C-4, 37.5 C-5, 55.3 —OCH_3 at phenyl ring; 99.4 C-9, 114.3 C-7; 136.2 C-8; 125.0–128.5 C-Arom.; 137.2, 140.3, 141.0, 142.4 *ipso*-C's; 158.3 C-3.

6-(4-bromophenyl)-4,5-dihydro-2,4-diphenyl-2H-indazol-3-ol. **30** IR (KBr) (cm^{-1}): 3401, 3092, 2998, 2926, 2831, 1606, 1525, 1437, 1348, 805, 713, 735; ^{1}H NMR (δ ppm): 2.92–2.95, 2.96–3.17 (m,2H,H_5), 4.02 (dd,1H,H_4, J = 11.8,9.5 Hz), 6.87 (d,1H,H_7, J = 8.8 Hz), 7.20–7.90 (m,14H,H-Arom.), 11.71 (s,1H,OH); ^{13}C NMR (δ ppm): 33.8 C-4, 37.4 C-5, 99.3 C-9, 114.3 C-7; 137.0 C-8; 116.1–137.0 C-Arom.; 142.1, 142.3, 149.0, 157.2 *ipso*-C's; 159.0 C-3.

4,5-Dihydro-2,4-diphenyl-6-p-tolyl-2H-indazol-3-ol. **31** IR (KBr) (cm^{-1}): 3421, 3060, 3053, 2927, 2833, 1601, 1512, 1440, 1372, 763, 715, 690; ^{1}H NMR (δ ppm): 2.92–3.18, 3.20–3.44 (m,2H,H_5), 2.28 (s,3H,CH_3 at phenyl ring); 4.01 (dd,1H,H_4, J = 11.1,8.8 Hz), 6.84 (d,1H,H_7, J = 8.4 Hz), 7.06–7.41 (m,14H,H-Arom.), 11.70 (s,1H,OH); ^{13}C NMR (δ ppm): 33.9 C-4, 38.7 C-5, 22.1 —CH_3 at phenyl ring; 99.4 C-9, 112.7 C-7; 134.1 C-8; 123.7–127.7 C-Arom.; 137.1, 140.6, 141.4, 157.3 *ipso*-C's; 159.2 C-3.

4,5-Dihydro-4-(4-methoxyphenyl)-6-(3-nitrophenyl)-2-phenyl-2H-indazol-3-ol. **32** IR (KBr) (cm^{-1}): 3427, 3020, 2924, 2851, 1607, 1523, 1487, 1446, 819, 714, 703; ^{1}H NMR (δ ppm): 2.94–3.28, 3.30–3.44 (m,2H,H_5), 3.82 (s,3H,OCH_3 at phenyl ring), 3.95 (dd,1H,H_4, J = 12.7,9.2 Hz), 6.85 (d,1H,H_7, J = 8.2 Hz), 7.00–8.44 (m,13H,H-Arom.), 11.82 (s,1H,OH); ^{13}C NMR (δ ppm): 34.4 C-4, 37.8 C-5, 99.5 C-9, 114.2 C-7; 135.2 C-8; 126.0–129.7 C-Arom.; 129.0, 131.4, 131.9, 139.2, 142.2 *ipso*-C's; 159.0 C-3.

Results and discussion

Chemistry

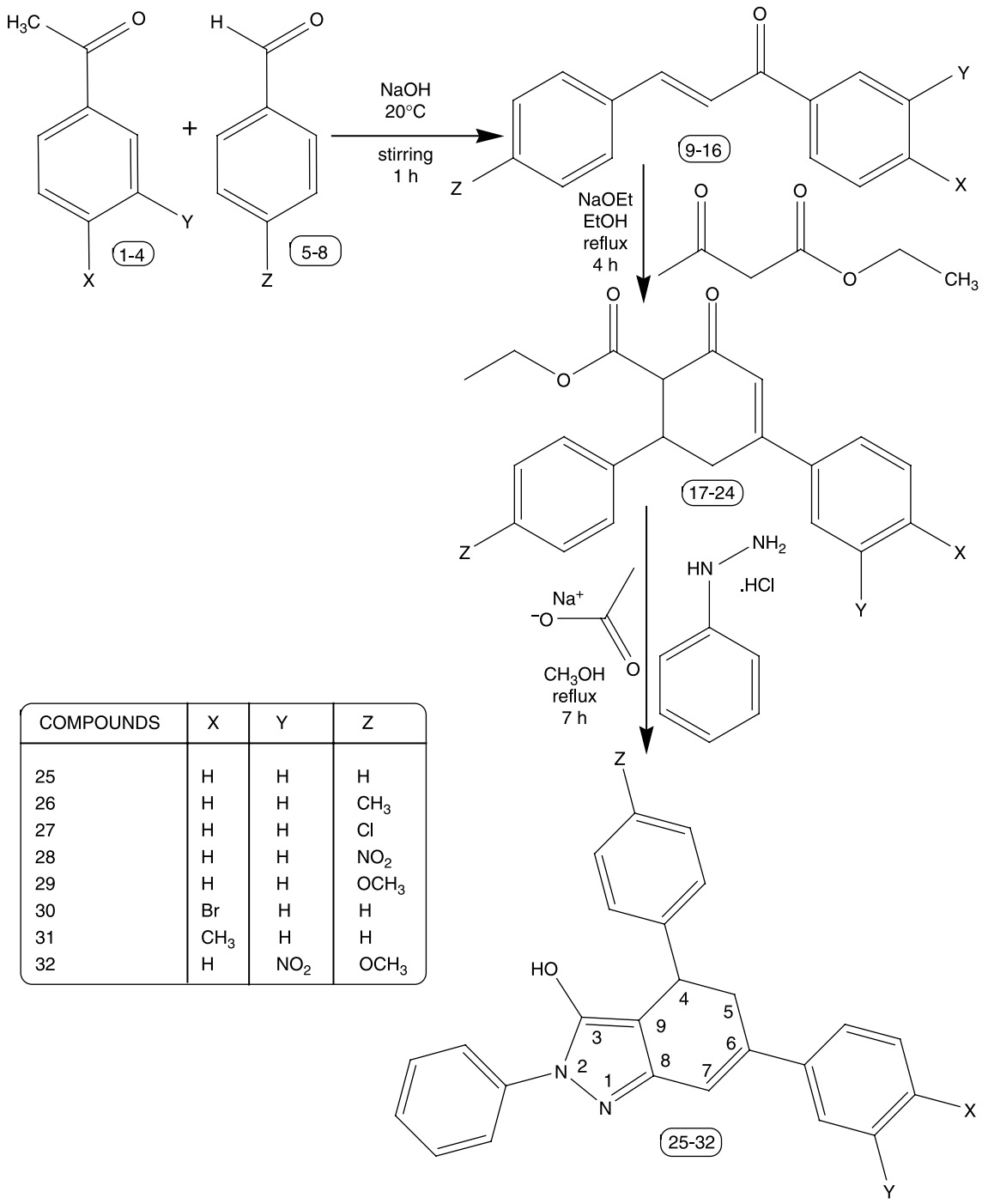
The schematic representation and analytical data for the synthesized compounds **25–32** are furnished in Scheme–1 and Table–I respectively. The synthetic strategy for the construction of 4,6-diaryl-4,5-dihydro-2-phenyl-2*H*-indazol-3-ols **25–32**, a new fused indazole derivative involves three steps, which is described as follows: Condensation of appropriate acetophenone **1–4** and appropriate benzaldehyde **5–8** in the presence of sodium hydroxide yields the respective 1,3-diaryl-prop-2-en-1-ones **9–16**. The respective α,β-unsaturated ketones **9–16** on treatment with ethyl acetoacetate in the presence of sodium ethoxide gives 6-carbethoxy-3,5-diarylcyclohex-2-enones **17–24** by Knoevenagel reaction. The formed ketones **17–24** on treatment with phenyl hydrazine hydrochloride and anhydrous sodium acetate in refluxing methanol gives 4,6-diaryl-4,5-dihydro-2-phenyl-2*H*-indazol-3-ols **25–32**. The structures of the compounds are elucidated by melting points, elemental analysis, MS, FT-IR, one-dimensional NMR (^{1}H & ^{13}C), D_2O exchanged ^{1}H-NMR, two-dimensional HSQC spectroscopic data.

Antibacterial activity

All the newly synthesized novel target molecule 4,6-diaryl-4,5-dihydro-2-phenyl-2*H*-indazol-3-ols, **25–32** were tested for their antibacterial activity *in vitro* against *S. aureus, β-H. streptococcus, V. cholerae, S. typhii, S. felxneri.* Minimum inhibitory concentration (MIC) in μg/mL values is reproduced in Table II. Ciprofloxacin was used as standard drug. Two compounds, which are having electron donating functional groups namely, (CH_3, OCH_3) **26** and **29** are potent against *S.aureus* and *β-H. streptococcus*. Compounds **27** and **28,** which have electron withdrawing -Cl and -NO_2 functional groups are active against *V.cholerae* and *S.typhii* than the standard drug Ciprofloxacin. Compound **32**, which contains both electron donating methoxy group and withdrawing nitro group is more potent against *S.typhii* and *S.felxneri*. In addition, compounds **30** and **31** with substituents in the 6-aryl ring are active against *S.felxneri* and for 31, *V.cholerae.*

Antifungal activity

The *in vitro* antifungal activity of the synthesized novel heterocyclic compounds, **25–32** was studied against the fungal strains viz., *A. flavus, Mucor, Rhizopus* and *M. gypsuem*. Fluconazole was used as a standard drug. Minimum inhibitory concentration (MIC) in μg/mL values is reproduced in Table III. In general, all the synthesized compounds exerted a wide range of modest *in vitro* antifungal activity against all the tested organisms, although the unsubstituted compound showed a poor spectrum. Of all the compounds tested,



COMPOUNDS	X	Y	Z
25	H	H	H
26	H	H	CH_3
27	H	H	Cl
28	H	H	NO_2
29	H	H	OCH_3
30	Br	H	H
31	CH_3	H	H
32	H	NO_2	OCH_3

Scheme 1. Reaction pathway for the synthesis of 4,5-Dihydro-2-phenyl-4,6-diaryl-2*H*-indazol-3-ols.

compounds **26, 29** and **31** are more effective against the tested *A. flavus* and *Rhizopus*. All these three compounds have electron donating methyl or methoxy functional groups. Compounds **27**, **28** and **30,** which contain electron withdrawing chloro, bromo or nitro groups in one of the rings, are potent against *Mucor* and M. *gypsuem*. Moreover, compound **32,** a unique one having both electron donating methoxy and electron withdrawing nitro functional groups in different rings is more effective against all the tested fungal strains than the standard drug, Fluconazole.

Conclusion

In conclusion, the different functionalities in 6-carbethoxy-3,5-diaryl-cyclohex-2-enone **17-24** can be used advantageously in the preparation of new 4,6-diaryl-4,5-dihydro-2-phenyl-2*H*-indazol-3-ols

Table I. Physical and analytical data of compounds 25-32.

Compound	Yield (%)	m.p. (°C)	Elemental analysis (%) C Found (calculated)	H Found (calculated)	N Found (calculated)	m/z ($M^{+\cdot}$) Molecular formula
25	80	237	82.35 (82.39)	5.49 (5.53)	7.64 (7.69)	(364) $C_{25}H_{20}N_2O$
26	75	242	82.47 (82.51)	5.82 (5.86)	7.36 (7.40)	(378) $C_{26}H_{22}N_2O$
27	76	251	75.22 (75.28)	4.78 (4.80)	6.98 (7.02)	(398) $C_{25}H_{19}Cl\ N_2O$
28	78	224	73.31 (73.34)	4.65 (4.68)	10.23 (10.26)	(409) $C_{25}H_{19}N_3O_3$
29	70	219	79.11 (79.16)	5.58 (5.62)	7.06 (7.10)	(394) $C_{26}H_{22}N_2O_2$
30	65	238	67.69 (67.73)	4.28 (4.32)	6.29 (6.32)	(443) $C_{25}H_{19}BrN_2O$
31	60	239	82.46 (82.51)	5.81 (5.86)	7.36 (7.40)	(378) $C_{26}H_{22}N_2O$
32	75	205	71.01 (71.06)	4.79 (4.82)	9.51 (9.56)	(439) $C_{26}H_{21}N_3O_4$

Table II. *In vitro* antibacterial activities (MIC) values for compounds 25-32.

Compound	Minimum *S.aureus*	Inhibitory *β-H.streptococcus*	Concentration *V.cholerae*	(MIC) *S. typhii*	in μg/mL *S. felxneri*
25	200	100	100	–	200
26	6.25	12.5	200	100	200
27	–	200	12.5	12.5	100
28	100	100	25	25	100
29	12.5	6.25	100	200	200
30	200	–	100	200	25
31	100	200	50	100	50
32	100	50	–	12.5	12.5
Ciprofloxacin	25	50	50	50	25

Table III. *In vitro* antifungal activities (MIC) values for compounds 25-32.

Compound	Minimum *A.flavus*	Inhibitory *Mucor*	Concentration *Rhizopus*	(MIC) in μg/mL *M. gypsuem*
25	200	100	200	100
26	12.5	–	12.5	–
27	100	25	200	25
28	100	50	100	25
29	12.5	200	12.5	200
30	100	50	100	12.5
31	25	200	25	100
32	25	25	12.5	6.25
Fluconazole	50	50	25	25

25-32. Examination of the *in vitro* antibacterial and antifungal activity profile in differently substituted novel title compounds, 4,6-diaryl-4,5-dihydro-2-phenyl-2*H*-indazol-3-ols **25-32** against the tested bacterial strains *viz*. *S. aureus, β-H. streptococcus, V. cholerae, S. typhii and S. felxneri,* and the fungal strains viz., *A. flavus, Mucor, Rhizopus* and *M. gypsuem* respectively gives a structure – activity relationship, albeit with a very limited number of compounds, which may be summarised as follows: the nature of substituent on the phenyl ring viz., methyl. methoxy, chloro, nitro as well as the bromo functions at the *meta* and *para* positions of the aryl moieties determine nature and extent of the activity of the synthesized fused indazolonol compounds. These observations may promote a further development of our research in this field. Further development of this group of fused indazolonol compounds may lead to compounds with better pharmacological profile than standard drugs.

Acknowledgements

Authors are thankful to NMR Research Centre, Indian Institute of Science, Bangalore for recording spectra. Two of our authors namely J.Thanusu and V. Kanagarajan are highly thankful for Annamalai University authorities for providing financial support in the form of Research Fellowship.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] Balasubramanian M, D'Souza A. Studies on the reduction of some substituted cyclohexanones. Tetrahedron 1968;24: 5399–5408.

[2] Cecchi L, Melani F, Filacchioni G, Tredici M. Synthesis and biological activity of some 3-(pyrazol-1′-yl)indazole derivatives Farmaco, 1984;39:945–952

[3] Ko JH, Yeon SW, Ryu JS, Yong KT, Ha SE, Jung YH, Eun PR, Kyu RC. Synthesis and biological evaluation of 5-arylamino-6-chloro-1*H*-indazole-4,7-diones as inhibitors of protein kinase B/Akt. Bioorg Med Chem Lett 2006;16:6001–6005.

[4] Gerpe A, Aguirre G, Boiani L, Cerecetto H, Gonzalez M, Olea-Azar C, Rigol C, Maya JD, Morello A, Piro OE, Aran VJ, Azqueta A, de Cerain AL, Monge A, Rojas MA, Yaluff G. Indazole *N*-oxide derivatives as antiprotozoal agents: Synthesis, biological evaluation and mechanism of action studies. Bioorg Med Chem 2006;14:3467–3480.

[5] Li X, Chu S, Feher VA, Khalili M, Nie Z, Margosiak S, Nikulin V, Levin J, Sprankle KG, Tedder ME, Almassy R, Appelt K, Yager KM. Structure-Based design, synthesis, and antimicrobial activity of indazole-derived SAH/MTA nucleosidase inhibitors. J Med Chem 2003;46:5663–5673.

[6] Selwood DL, Brummell DG, Budworth J, Burtin GE, Campbell RO, Chana S, Charles IG, Fernandez PA, Glen RC, Goggin MC, Hobbs AJ, Kling MR, Liu Q, Madge DJ, Meillerais S, Powell KL, Reynolds K, Spacey GD, Stables JN, Tatlock MA, Wheelers KA, Wishart G, Woo C. Synthesis and biological evaluation of novel pyrazoles and indazoles as activators of the nitric oxide receptor, soluble guanylate cyclase. J Med Chem 2001;44:78–93.

[7] Gopalakrishnan M, Sureshkumar P, Thanusu J, Kanagarajan V, Govindaraju R, Jayasri GA. A convenient 'one-pot' synthesis and in vitro microbiological evaluation of novel 2,7-diaryl-[1,4]-diazepan-5-ones. J Enz Inhib Med Chem 2007;22:709–715.

[8] Gopalakrishnan M, Sureshkumar P, Thanusu J, Prabhu C, Kanagarajan V. One-pot conversion of piperidine-4-ones to [1,4]-diazepan-5-ones under microwave irradiation using silica gel supported $NaHSO_4$ catalyst. J Chem Res 2007;2:80–81.

[9] Gopalakrishnan M, Sureshkumar P, Kanagarajan V, Thanusu J. Design, 'one-pot' synthesis, characterization, antibacterial and antifungal activities of novel 6-aryl-1,2,4,5-tetrazinan-3-thiones in dry media. J Sulf Chem 2007;28:383–392.

[10] Balasankar T, Gopalakrishnan M, Nagarajan S. Synthesis and anti-bacterial activity of some 5-(4-biphenyl)-7-aryl[3,4-d]-1,2,3-benzoselenadiazoles. J Enz Inhib Med Chem 2007;22: 171–175.

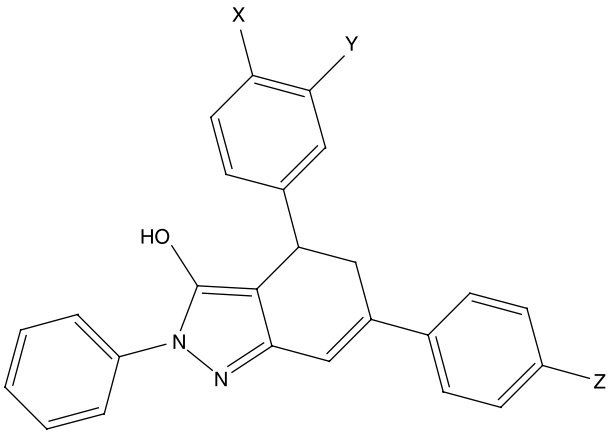
[11] Balasankar T, Gopalakrishnan M, Nagarajan S. Synthesis and antibacterial activity of some 5-(4-biphenylyl)-7-aryl[3,4-d] [1,2,3]-benzothiadiazoles. Eur J Med Chem 2005;40:728–731.

[12] Dhar MH, Dhar MM, Dhawan BN, Mehrotra BN, Ray C. Screening of Indian plants biological activity. Part I. Indian J Exp Biol 1968;6:232–247.

[13] Guthrie W, Wang XP. The aldol condensation of acetophenone with acetone. Can J Chem 1991;69:339.

[14] Guthrie W. Rate-equilibrium correlations for the aldol condensation: an analysis in terms of Marcus theory. J Am Chem Soc 1991;113:7249.

[15] Nielson AT, Houlihan WJ. The aldol condensation. Org React 1968;16:1–438.



4,6-DIARYL-4,5-DIHYDRO-2-PHENYL-2*H*-INDAZOL-3-OL
NOVEL FUSED INDAZOLES