The davis-beirut reaction: a novel entry into 2*H*-indazoles and indazolones. Recent biological activity of indazoles

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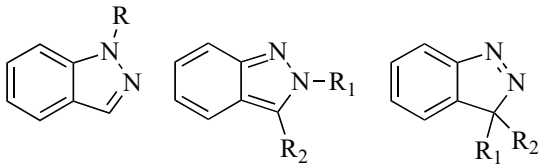
Abstract: A novel, easy method for the syntheses of richly diversified 2*H*-indazoles and indazolones, called the Davis-Beirut reaction, and other recent 2*H*-indazole synthetic routes are briefly reviewed. An update on the biological activity of indazoles is also surveyed.

Keywords: 2*H*-indazoles, Biological Activity, Davis-Beirut reaction, Indazolone.

INTRODUCTION

The purpose of this review [1] is twofold: (1) introduction of recent developments in the chemistry of 2*H*-indazoles (Fig. **1**) with a focus on the synthesis of these interesting heterocycles via the Davis-Beirut reaction, and (2) an update on recent advances of indazole biological activities. It is well recognized that 2*H*-indazoles are not the most widely investigated of the three indazole isomers (**1**, **2**, and **3**) and, presumably because of the challenges related to their synthesis and hence availability, only a few non-patent recent reports are available regarding their biological activity.



1 **2** **3**

Fig. (1). 1*H*-, 2*H*-, and 3*H*-indazole isomers.

Two useful reviews [2] addressing the synthesis of 1*H*- and 2*H*-indazoles appeared recently. These two reviews focus on synthetic approaches to indazoles and none of the 2*H*-indazole synthetic methods in those two reviews will be repeated here; neither review cites any examples of the Davis-Beirut reaction, so this chemistry will be reviewed here.

SECTION 1. THE DAVIS-BEIRUT REACTION: NOVEL AND EASY ACCESS TO 2*H*-INDAZOLES AND INDAZOLONES:

Over the past seven years, we have been interested in methods development for the synthesis of 2*H*-indazoles and their subsequent chemical reactions, especially their conversion to indazolones. Our efforts were realized through the construction of the N-N bond of the pyrazole moiety of 2*H*-indazoles from o-nitrobenzyl amines. This methodology has proven adept at the construction of a variety of substituted 2*H*-indazoles and indazolones, which, as will be demonstrated below, other methods cannot match due to inherent limitations. This N,N-bond forming heterocyclization methodology has been named the Davis-Beirut reaction [3] in recognition of the merits of international collaboration.

Scheme **1** demonstrates two general methods for construction of the starting material, namely, an *o*-nitrobenzyl amine (**6**), which is replete with the requisite functionality for the Davis-Beirut reaction. Heating *o*-nitrobenzlamine (**6**) with 5% KOH and an appropriate primary alcohol leads to the desired di-, tri-, or tetra-substituted 2*H*-indazole [4]. Subsequently, a library of approximately two hundred 2-alkyl-3-alkoxy-2*H*-indazoles was synthesized using parallel solution phase methods. Furthermore, it was found that addition of a controlled amount of water to the alcoholic solvent had a critical effect on the yield of the reaction [5].

Substrate diversity in the Davis-Beirut reaction (Schemes **2** and **3**) presents itself in the numerous heterocycles that can easily be fused to the 2*H*-indazole core. Heterocycles such as these would be difficult to prepare by other methods [6]. The Davis-Beirut reactions delineated in (Scheme **3**) underscore the ease of the reaction – all products were prepared by a one-pot process starting with the appropriate nitro aldehyde – and synthetic versatility of the process [3b].

SECTION 2. OTHER RECENT METHODS FOR THE SYNTHESIS OF 2*H*-INDAZOLES:

Additional new and elegant methods with ease of reaction and/or often high yields for the synthesis of 2*H*-indazoles have recently been reported (Scheme **4**). Collectively, these methods are complimented by the synthetic versatility of the Davis-Beirut reaction in two aspects: (1) several encounter limited synthetic scope and, more importantly, (2) all lack the 3-alkoxy moiety installed

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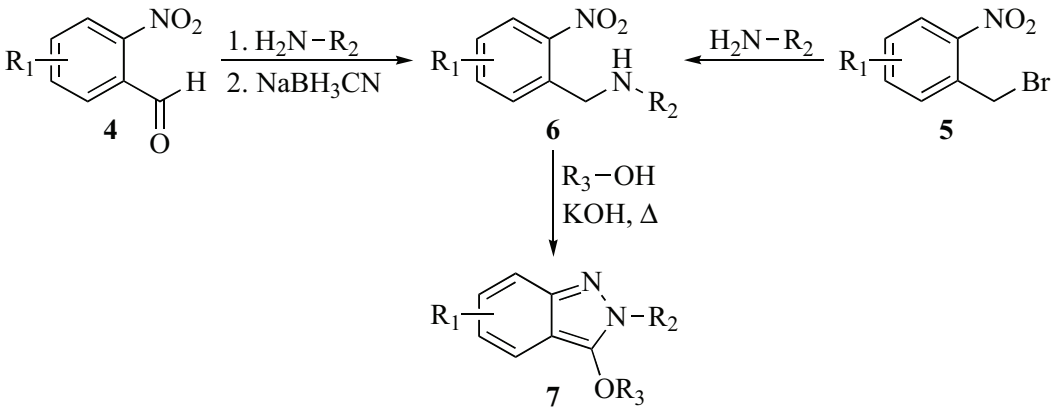
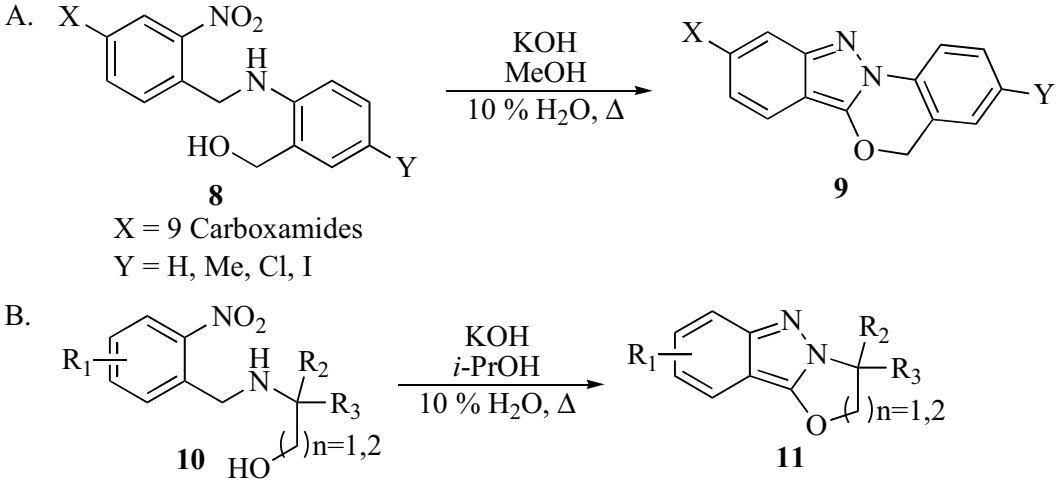
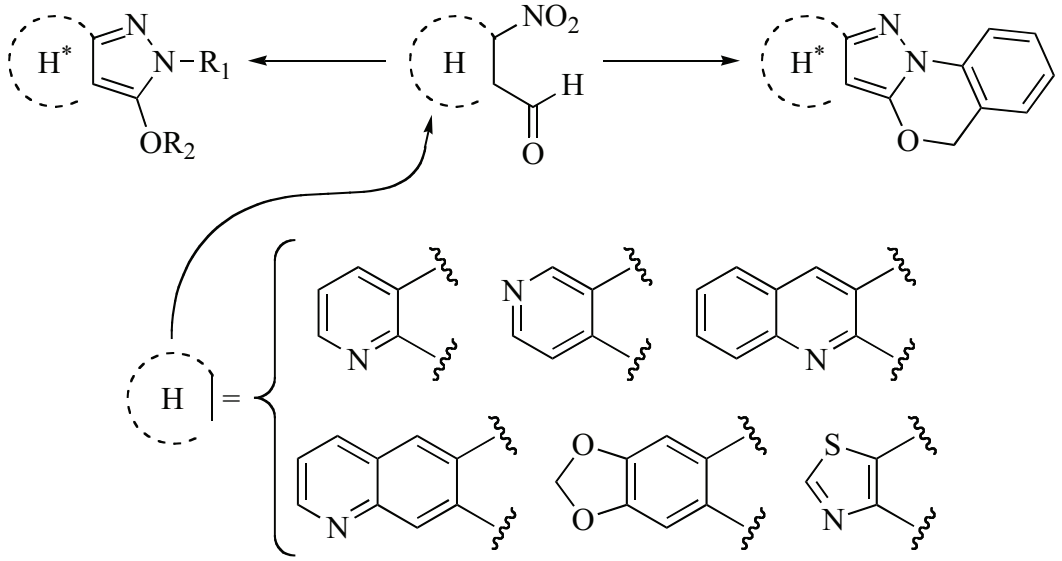


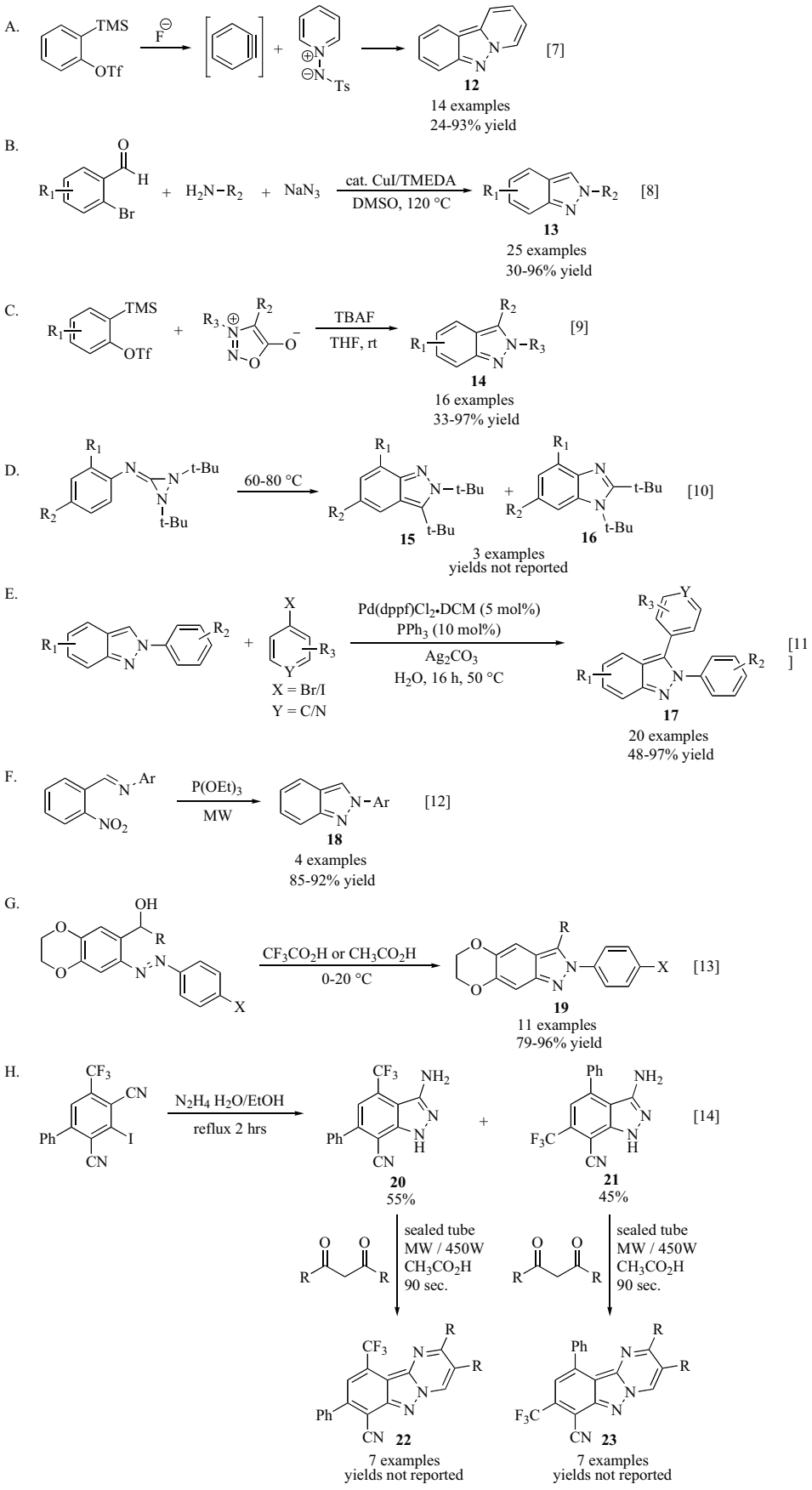
Scheme (1). The Davis-Beirut reaction: one-pot N-N bond forming heterocyclization.



Scheme (2). The Davis-Beirut reaction: a route to indazolo-fused heterocycles.



Scheme (3). Heterocycle-fused 2*H*-indazoles synthesized by the Davis-Beirut reaction.

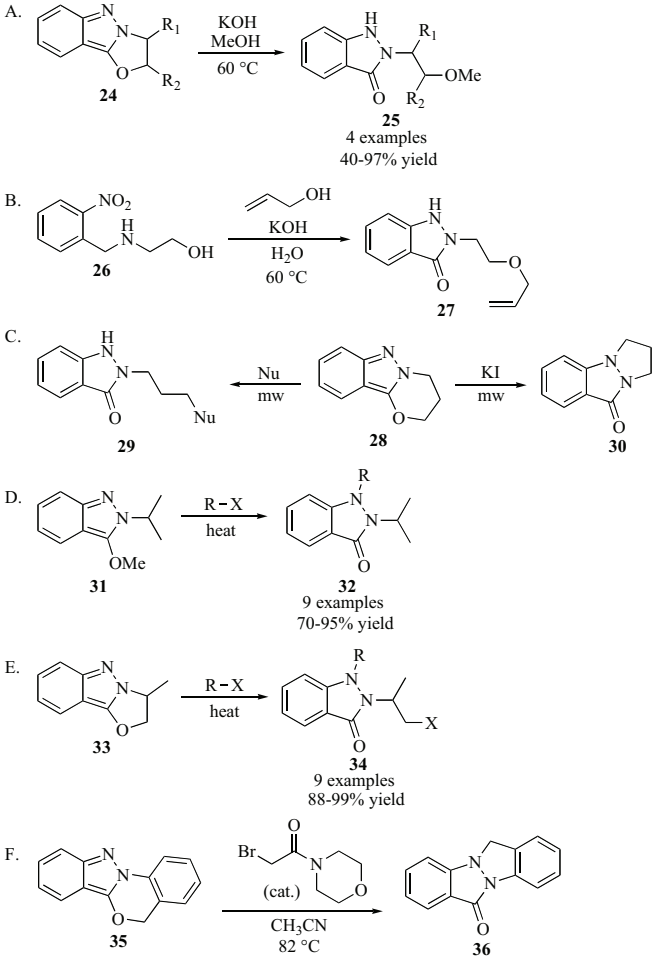


Scheme (4). Additional recently published routes to 2*H*-indazoles.

by the Davis-Beirut reaction. Consequently, the conversion of these 2*H*-indazole derivatives into indazolones is difficult to achieve via these methods.

Section 2.1. Conversion of 2*H*-indazoles to indazolones

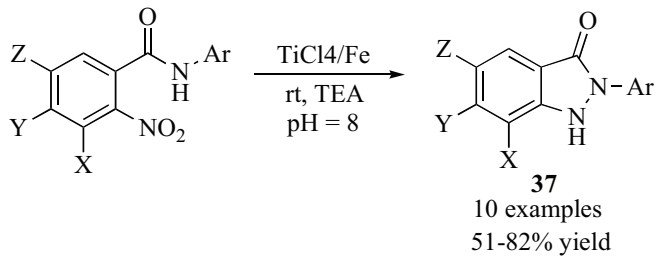
3-Alkoxy derivatives of 2*H*-indazoles, prepared in straightforward fashion by the Davis-Beirut reaction, can be converted to 1*H*-indazolones in good to high yields. (Scheme **5**) illustrates this reaction, which can take place using nucleophilic or electrophilic protocols [15]. It is noteworthy that the formation of 3-alkoxy-2*H*-indazole vs. 2-*N*-alkyl substituted 1*H*-indazolone in the Davis-Beirut reaction is dependent on the reaction conditions specified in the relevant publications. Additionally, reactions of 2*H*-indazoles **28** (Scheme **5C**) and **35** (Scheme **5F**) resulted in their unprecedented rearrangements to 1*H*-indazolones **30** (ANRORC) [15b, 16] and **36** (AERORC) [3a], respectively.



Scheme (5). Conversion of 2*H*-indazoles to 1*H*-indazolones.

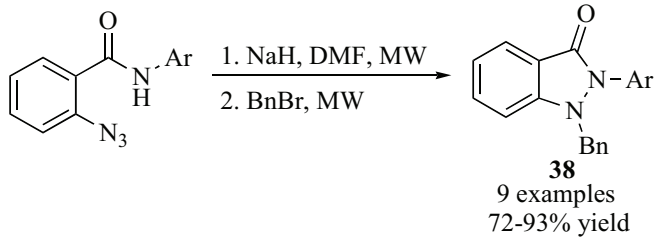
Section 2.2. Other Recent Methods for the Synthesis of 1*H*-indazolones

The reduction of *o*-nitrobenzanilide with low-valent titanium leads to 1*H*-indazolones [17]. This reaction is pH dependent and limited to *N*-aryl substituted *o*-nitrobenzanilides (Scheme **6**).

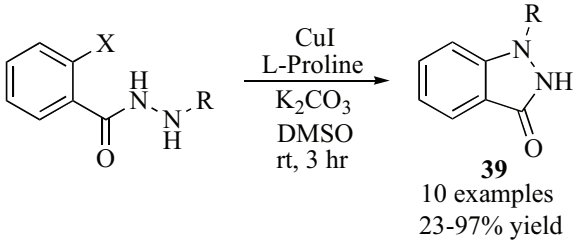


Scheme (6). Conversion of 2*H*-indazoles to 1*H*-indazolones.

Microwave-assisted nucleophilic substitution of *o*-azidobenzanilides, catalyzed by NaH in DMF, gives 1,2-disubstituted 1*H*-indazolones (Scheme **7**) [18]. Also, the cyclization of 2-halobenzoic *N*-substituted hydrazides to 1-substituted 1*H*-indazolones has been reported as shown in (Scheme **8**) [19]. Unlike the Davis-Beirut reaction, substituent variation is limited in most reported cases to positions 1 and 2 of the indazolone structure.



Scheme (7). Microwave-assisted nucleophilic substitution of *o*-azidobenzanilides.



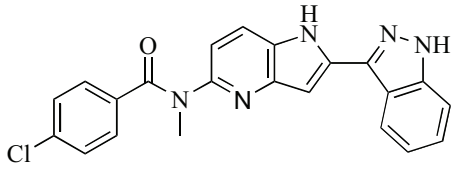
Scheme (8). Cyclization of 2-halobenzoic *N*-substituted hydrazides to form indazolones.

SECTION 3. BIOLOGICAL ACTIVITY OF INDAZOLES:

Although this review was initially intended to address recent trends in both the synthesis and biological activity of 2*H*-indazoles, it became evident that, aside from some patented literature, little work has been reported on the latter's biological activity. One major factor behind this tardiness, we believe, is the challenge of synthesizing diversely substituted 2*H*-indazoles; a challenge effectively alleviated by the discovery of the Davis-Beirut reaction and the other methods cited in this review. In light of the recent excellent review [20] on the pharmacological properties of indazole derivatives, we present here an update and include the recent, but limited, biological activity reports concerning 2*H*-indazoles.

Section 3.1. Anticancer Activity

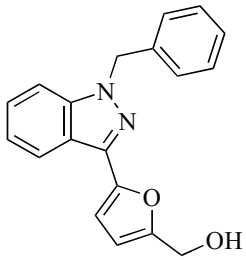
Using an MTT assay, which measures cell viability and proliferation, *N*-(2-(1*H*-indazol-3-yl)-1*H*-pyrrolo[3,2-b]pyridin-5-yl)-4-chloro-*N*-methylbenzamide (**40**, **SMT-A07**, Fig. **2**) increased the rate of apoptosis in human leukemia HL60 cell lines from 6.9 to 49.7% and from 8.7 to 56.3% in NB4 cell lines. It appears that **SMT-A07** down regulates and cleaves procaspase-8, procaspase-3, BID, as well as PARP and cleaved caspate-8, caspase-3, and PARP (cleaved fragment) [21].



40, SMT-A07

Fig. (2). SMT-A07: activity against human leukemia cell lines.

Using an MTT assay, indazole derivative 1-benzyl-3-(5-hydroxymethfur-2-yl)indazole (**41**, **YC-1**, Fig. **3**) was found to have *in vitro* activity against human lung cancer cell line NCI-H226 in an MTT assay. The mechanism of action involves suppression of protein levels of cyclin D, CDK2, and CDC 25A. Furthermore, it increased the number of NC1-H226 cells in the G0/G1 phase of the cell cycle and up-regulated p16, p21, and p53. It was concluded that long exposure to **YC-1** induced apoptosis by a mitochondrial-dependent pathway [22].



41, YC-1

Fig. (3). YC-1: activity against human lung cancer cell line, NCI-H226.

Antiproliferation activity against cell lines derived from human pancreatic carcinoma, human breast adenocarcinoma, and human colorectal adenocarcinoma was exhibited by all three indazole derivatives **TH-337**, **TH-482**, and **TH-494** (**42-44**, respectively, Fig. **4**). The data from a structure-activity relationship (SAR) study showed that the combination of the indazole core and acetylene moiety at position C-7 was important for activity. Using the HUVEC cell line, it was shown that the antiproliferative activity of **TH-482** was due to cell cycle arrest at the G_2lM phase. This indazole derivative (**TH-482**) was reported to be an effective, novel tubulin-targeted antiproliferative and antivascular agent, and more effective *in vitro* than the benchmark antiproliferative Combretastatin A-4 [23].

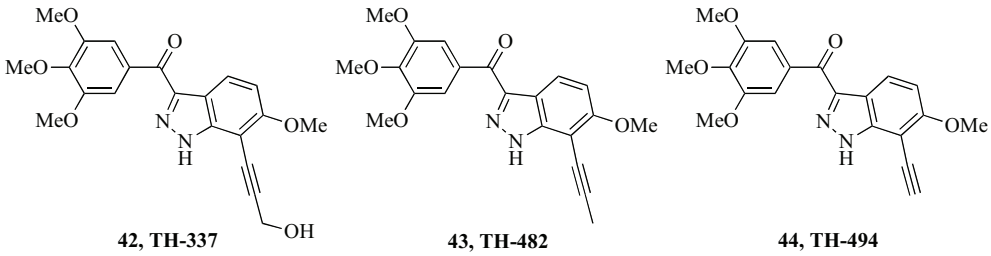
A host of novel substituted pyrimido[1,2-b]indazoles (Fig. **5**) were found to be active in an *in vitro* MTT assay against A-549 epithelial cells and more effective than Etoposide (**46**, Fig. **5**), a known anti-cancer agent. Based on the structure-activity relationship (SAR) data, the authors concluded that the presence of a trifluoromethyl group on the pyrimidine ring along with a phenyl ring or another trifluoromethyl group was important for activity. Pyrimido[1,2-b]indazole **45** was the most active in this series [14].

2*H*-Indazoles **47** (R=Cl, Fig. **6**), **48** (R=CH_3) and **49** (R=OCH_3) showed improved activity compared to Saframycin **YD-3**, a compound with known anti-angiogenic activity, when tested on the vascular endothelial growth factor (VEGF)-induced cell proliferation of human umbilical vein endothelial cells (HUVECs). The SAR data indicates that the presence of a benzyl group on *N*2 with substitution in the para position is important for activity. Moreover, in an in vivo plug assay, 2*H*-indazoles **47**, **48**, and **49** demonstrated significant anti-angiogenic effects, which were superior to the positive control of **YD-3** [24]. In a QSAR study employing the crystal structure of tubulin, calculated binding energies for 2H-indazoles **47-49** correlated well with the respective experimental inhibitory effects.

Section 3.2. Cardiovascular Risk

Section 3.2.1. Arterial Thrombosis

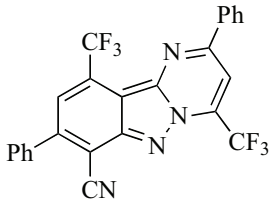
Ethyl 4-[1-(3-chlorobenzyl)-1*H*-indazol-3-yl) benzoate (**51**, R = Cl, Fig. **7**) showed potent inhibitory effects on PAR4-mediated platelet aggregation, ATP release, and P-selection expression. Analog **50** (R=H, **YD-3**, Fig. **7**) exhibited dual inhibitory effects on PAR4 and thromboxane formation from arachidonic acid. Using **YD-3** (Fig. **6**) as the lead compound, 80 indazole derivates were synthesized and tested for their selective anti-PAR4 activity. From a



42, TH-337 **43, TH-482** **44, TH-494**

Fig. (4). TH-337, **TH-482**, and **TH-494**: Antiproliferative activity against cell lines derived from human pancreatic carcinoma, human breast adenocarcinoma, and human colorectal adenocarcinoma.

structure-activity relationship (SAR) study, it was concluded that the 4-ethoxycarbonyl and the benzyl group of **YD-3** were important functional groups for the observed anti-PAR4 activity of **YD-3**. Substitution of the ethoxycarbonyl group of **YD-3** with other esters, amides, acarboxylic acid, or carbinol moieties decreased the activity significantly. Introduction of chloro, fluoro, or methoxy functional substituents on the benzyl group of **YD-3** led to variable results [25].



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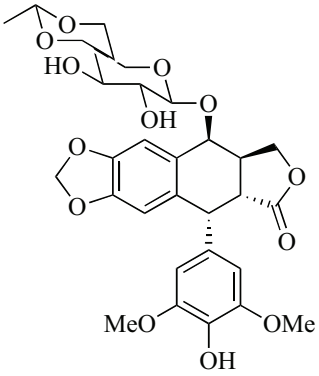
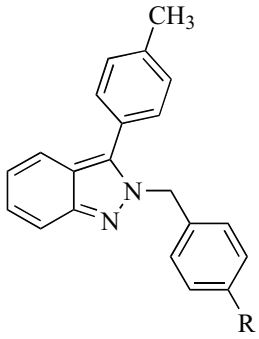
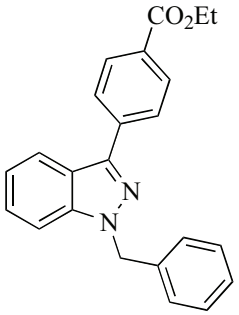


46, Etoposide

Fig. (5). Pyrimido[1,2-*b*]indazole **45:** activity against epithelial cancer cell line A-549.



47, R = Cl
48, R = CH_3
49, R = OCH_3

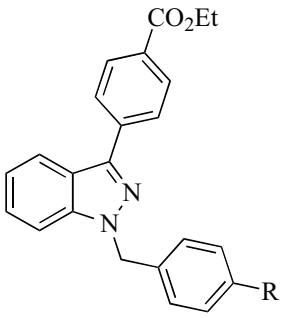


50, YD-3

Fig. (6). 2-Benzyl-3-(4-methylphenyl) **47**, **48**, and **49**, and **YD-3**: anti-angiogenic activity against HUVECs.

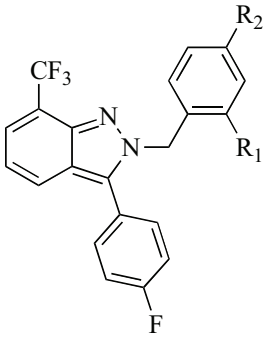
Section 3.2.2. Atherosclerosis

2-Benzyl-3-aryl-7-trifluoromethyl 2*H*-indazoles **52** (R^1=F, R^2=H, Fig. **8**) and **53** (R^1=Cl, R^2=F, Fig. **8**) showed less lipid accumulation in HepG2 cells than references (human heptocellular liver carcinoma cell line), while 2*H*-indazole **52** reduced aortic lesion area in LDLR (low density lipoprotein receptor). It was also reported that, in mice, the loss of LXR (liver X receptor) increases atherosclerosis, whereas treatment of mice with LXR agonist might eventually result in reduction of the risk of cardiovascular disease [26].



50, R = H **(YD-3)**
51, R = Cl

Fig. (7). Ethyl 4-[1-(3-chlorobenzyl)-1*H*-indazol-3-yl) benzoate and **YD-3**: activity against arterial thrombosis.



52, R1 = F, R2 = H
53, R1 = Cl, R2 = F

Fig. (8). 2-Benzyl-3-aryl-7-trifluoromethyl 2*H*-indazoles **52** and **53**: prevent lipid accumulation in HepG2 cells.

Section 3.2.3. Antihypertension

1-[Imidazolidin-2-yl)imino-7-methylindazole **54** (Fig. **9**) and other related indazoles were found to act as antihypertensive agents. From a structure-activity relationship (SAR) study, the authors concluded that the placement of an iminoimidizolidine moiety on *N*1 in combination with a methyl group at position C7 were important for binding activity. Some of these derivatives were reported to be selective α_2-adrenoceptor ligands with high α_2-adrenoceptor/imidazoline I receptor selectivities [27].

Section 3.3. Inhibitors of Nitric Oxide Synthase (NOS)

Nitric oxide synthase catalyzes the oxidation of *L*-arginine to *L*-citruline and nitric oxide (NO), an important agent in blood pressure regulation, neurotransmission, and immune response. e-Nitroindazoles, especially 7-nitroindazole, are strong inhibitors of nitric oxide synthase (NOS). The spectroscopic properties (including x-ray diffraction) of three NOS inhibitors (Fig. **10**) have recently been reported [28].

In an earlier report, these workers, in pursuit of neuroprotective activity and NOS-I/NOS-II selectivity, synthesized 14 substituted 1*H*-indazoles and 2*H*-indazoles

and found that 4,5,6,7-tetrafluoro-3-methyl-1*H*-indazole (**58**, Fig. **11**) inhibited the activities of NOS-I by 63% and NOS-II by 80%. In contrast, 4,5,6,7-tetrafluoro-3-perfluorophenyl-1*H*-indazole (**59**, Fig. **11**) inhibited NOS-II activity by 80%, but had no effect on NOS-I activity [29]. It is believed that the aromatic indazole moiety is important in NOS inhibition and bulky groups or *N*-methylation diminish the effect. Furthermore, fluoro substituents on the aromatic ring increased the inhibitory effect as well as the NOS-II selectivity.

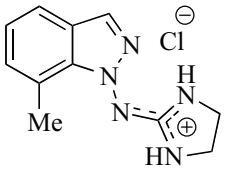


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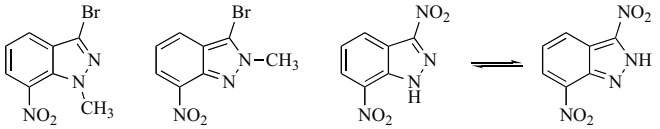
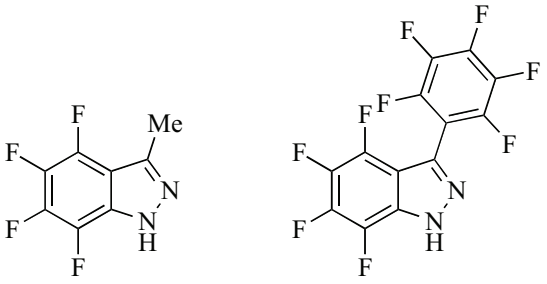
Fig. (9). 1-[Iimidazolidin-2-yl)imino-7-methylindazole **54**: antihypertension activity.



55 **56** **57a** **57b**

Fig. (10). Indazoles **55**, **56**, and **57**: NOS inhibitors.



58 **59**

Fig. (11). NOS-I/NOS-II Inhibitor **58** and NOS-I Inhibitor **59**.

Calculations at the M05-2x/6-311+G(d) level offer an explanation for the affinity of indazoles for nitric oxide synthases using simplified porphyrin models. These calculations predict that 3,7-dinitro-1*H*-indazole should be a good NOS inhibitor [30]. Introduction of a bromo or nitro substituent at the C4 position of the 1*H*-indazole yields a compound almost as potent as 7-nitroindazole [31]. 7-Nitroindazole was also identified as an anticonvulsant agent; however, this flufosinate-induced convulsion property does not involve neuronal nitrogen oxide synthase [32].

Section 3.4. Male Contraceptive Activity

The search for male contraceptive drugs has been encouraged by many health organizations. Two recent studies have shed more light on this important issue in the development of indazole derivatives, which have shown promise as male contraceptives in rat experiments [33]. At a single 6 mg/Kg dose of gamendazole (**60**, Fig. **12**), seven out of seven rats became infertile after 3 weeks. Upon withdrawal of compound, fertility returned by 9 weeks in four of seven animals. The binding targets were identified as HSP90AB1 (previously known as HSP90beta [heat shock 90-kDa protein 1, beta]) and EEF1A1 (previously known as eEF1A, eukaryotic translation elongation factor 1 alpha 1). Gamendazole interaction with HSP90AB1 and EEF1A1 is believed to be behind the loss of spermatids and, therefore, infertility.

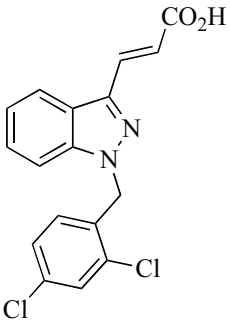


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Fig. (12). Gamendazole: activity against HSP90AB1 and EEF1A1.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

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[1] Dedicated to the memory of Professor Costas H. Issidorides (Deceased, Nov. 13, 2010).

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